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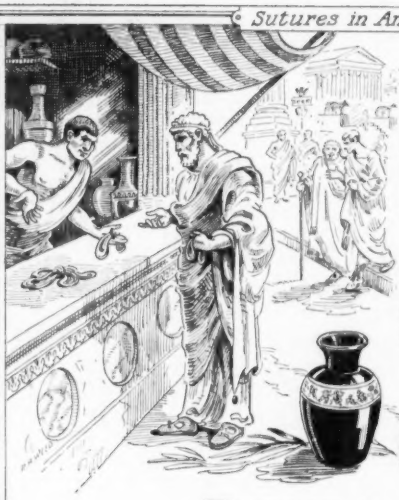

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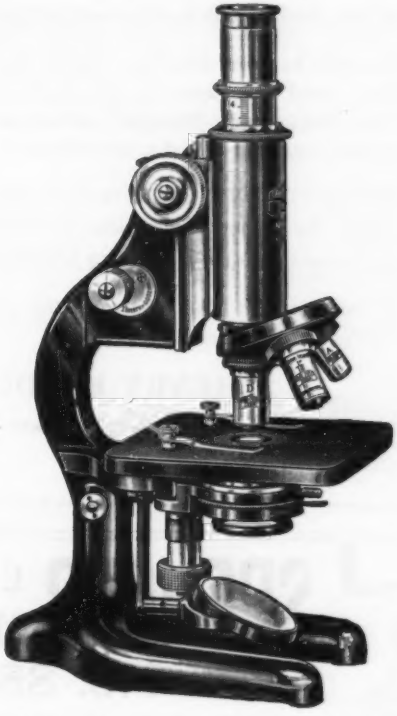

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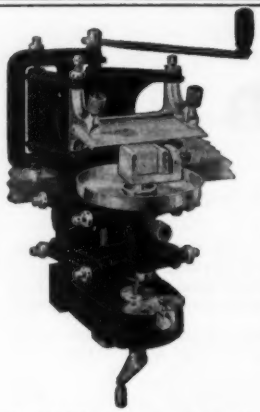

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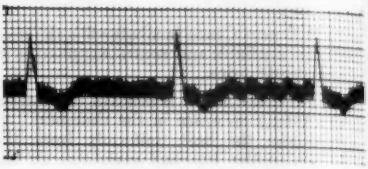

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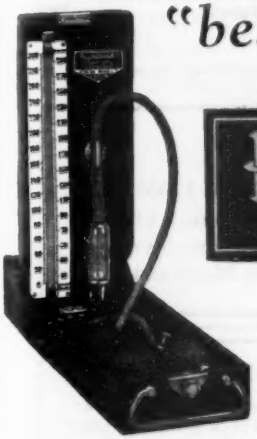

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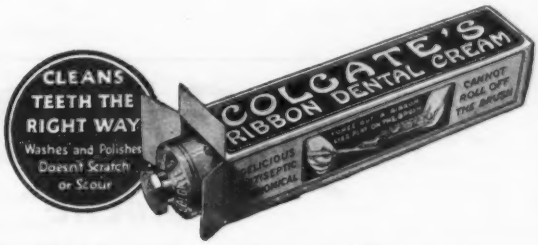

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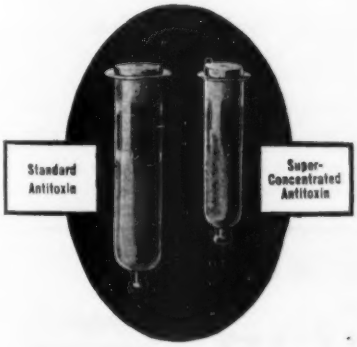

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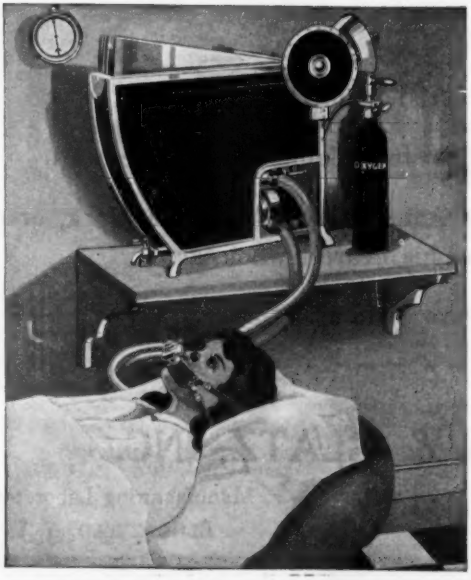

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DECEMBER, 1923

ORIGINAL ARTICLES.

OBSERVATIONS UPON THE NATURE, DIAGNOSIS AND CLINICAL MANAGEMENT OF GASTRIC ULCER WITH SUGGESTIONS FOR A RATIONAL REGIMEN OF TREATMENT.*

By Frank Smithies, M.D., F.A.C.P.,

PROFESSOR OF MEDICINE, UNIVERSITY OF ILLINOIS, SCHOOL OF MEDICINE; PHYSICIAN-IN-CHIEF TO ST. ELIZABETH HOSPITAL, CHICAGO.

Introduction. It requires but a casual acquaintance with the literature of peptic ulcer to demonstrate that treatment of the affection has been largely empirical. Various types of therapy appear to have obtained a vogue because their application relieved symptoms or for a time appeared to delay a fatal outcome. Success of modes of treatment has been judged from its effect upon the immediate condition and not with respect to the ultimate course of the ailment. Statistics of hospitals or private practices rarely indicate the condition, digestively, of patients treated after five to twenty-five-year intervals following a particular mode of therapy. As a rule, hospital records state that a peptic-ulcer patient has been discharged "cured," "improved," "not improved," or has "died." With exception of the fatal cases, usually facts are not available regarding the future course of the disease, inasmuch as patients frequently seek the advice of another physician, should their disability return after a long and expensive course of treatment at the hands of one physician. It is also of interest to observe that of a half dozen *experts* non-surgically treating peptic ulcer by radically different regimens, the percentages of *cure* show a variation of but five to ten points. I have also been impressed by the

* Oration in Medicine, Virginia State Medical Association, Norfolk, Va., November 1, 1922.

fact that at the most competent hands, certain ulcers alike resisted all types of treatment. It has seemed to me that unsatisfactory as the treatment of peptic ulcer might be, it should be possible to devise a type of management that at least had the merit of resting upon certain basic principles. It likewise appears to me that methods of therapy should be based upon information that has been returned by modern histological, physiological and clinical investigation. All too frequently the mind, medical, has confused *kur* (a form of clinical management) with *cure*, the actual eradication or substantial healing of a pathological lesion.

The Nature of the Problem. The problem is not a simple one, even though for some eighty years attempts have been made by numerous clinicians to have it appear as such. Those observers who, either by pathological, chemical or clinical training, are most competent to speak, admit that facts are not yet at hand which really permit our making unqualified statements with regard to either the cause, course or cure of the ailment.

Clinically, peptic ulcer is a disease which may or may not exhibit symptoms or signs. It is an ailment which, in its uncomplicated form, may be so closely mimicked clinically by non-ulcerous dyspepsias as to deceive the most experienced diagnostician. Until complications occur, it is a disease characterized in 84 per cent of instances by a peculiar *periodicity*. It frequently manifests itself by recovery and relapse wholly independent of type or duration of treatment. It is associated with a form of gastric malfunction, the cessation of which does not necessarily indicate eradication of its exciting causes. It is a disease about which little prophecy respecting its extent or its future course can be made from its clinical symptomatology. Acuteness of symptoms does not wholly indicate the histopathological changes existing at the diseased focus; acute manifestations, histologically, can complicate chronic inflammatory lesions pathologically. The most serious clinical outcome may follow upon *spontaneous* or so-called *therapeutic* cure, accompanied by the subsidence of the initial dyspeptic upset. Stenosis, gastric malformation, involvement of extragastric viscera, fatal hemorrhage, or malignant transformation may occur with comparatively slight clinical manifestations or certainly with relatively little change in the patient's complaints. Peptic ulcer is an ailment indistinguishable, clinically, from the appearance of beginning gastric cancer, or gastric involvement by syphilis, or tuberculosis. It is a disease which but rarely occurs in individuals not already affected with other clinical abnormalities, as infections about the head, throat and neck, abdominal diseases, *i. e.*, inflammatory changes in the appendix, gall-bladder, perigastric lymph nodes, pelvic structures; disturbances in the circulatory, eliminative, nervous or lymphatic symptoms or malfunctions of that group of glands concerned with food digestion and assimilation. Finally,

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it is an ailment of almost universal distribution, and one capable of producing such disturbances of the physical and mental health, as to demand relief.

Etiology. A study of the affection demonstrates that a narrow conception of the etiology of peptic ulcer is quite erroneous. Competent observers have experimentally produced gastric ulcer by a wide variety of methods. It has been shown that gastric ulcers differing slightly in type, histologically, can be caused more readily from the systemic than from the local intragastric point of attack. Some of the more familiar causative agents are: (*a*) Bacteria of various types and strains, the evidence apparently indicating that any organism capable of multiplying in the blood and lymph streams and being viably implanted in the stomach's or duodenal's wall may furnish the beginning of ulcers; (*b*) bacterial toxins; (*c*) cutaneous burns; (*d*) elements of metabolic origin (Bolton's "gastrotoxin" injected intraperitoneally or subcutaneously); (*e*) metallic and alkaloidal poisons; (*f*) poisons introduced directly into the stomach (corrosives, caustics); (*g*) alterations in the stomach's circulation (vascular blocking, adrenalectomy, thrombi, emboli, arteriosclerosis or nervous imbalance, external pressure); (*h*) artificial pyloric spasm or stenoses; (*i*) mechanical trauma and food or foreign protein intoxications. But whatever may be the experimental mode of production, the ulcers resulting differ slightly. The lesions produced which are essentially similar from all causes are: Local inflammatory edema, loss of surface epithelium, minute or gross hemorrhage, necrosis, glandular destruction and frequently secondary infection. In the healing of ulcers, irrespective of the way that they may have been produced, the basic features consist in development of protective connective tissue by hyperplasia with resultant scar. Ulcers in which the underlying causative agents persist constantly or become intermittently active heal the most slowly. It is by such incomplete attempts at repair that, from so-called *acute* beginnings, pathological chronicity is induced. Recently I have summarized, clinically, what appeared to be etiological factors associated with 522 proved, histologically, chronic gastric ulcers:

TABLE I.

Group.	No. of cases.	Per cent.
1. Infections (chronic and acute)	173	33.7
2. Arteriosclerosis (with vascular hypertension, 56 cases; without vascular hypertension, 21 cases)	77	14.7
3. Visceral hypertonia (vagus or splanchnic hyperfunction)	68	13.0
4. Chronic general anemia (so-called "chlorotic")	61	11.3
5. Syphilis	41	7.8
6. Visceral hypotonia (vagus or splanchnic hypofunction)	27	5.2
7. Postoperative	27	5.2
8. Industrial intoxication (occupational poisonings)	22	4.2
9. Metabolic dysfunction (thyroid, suprarenal, pituitary, etc.)	18	3.4
10. Trauma (abdominal injury from blows, falls, etc.; intragastrically, foreign bodies)	8	1.5

To the seriously inclined student of peptic ulcer and its clinical management, the classifications given will prove of a certain suggestive value and furnishes significant hints respecting the possibilities of the various so-called *curative* regimens. It is quite likely that similar constitutional disturbances are associated with duodenal ulcer.

The summary given indicates that, with the evidence at hand, one cannot expect to establish a single definite cause of peptic ulcer. Seemingly, the exciting and localizing causes of ulcers vary widely and are individual for each subject. The essential point is that, through some systemic, and later local gastric malfunction, a point of least resistance occurs in the mucous membrane and normal gastric physiology is permitted to produce an *abnormal* tissue change. It would likewise appear that we have no basis for regarding peptic ulcer as a distinct disease entity. It seems more proper to consider that ulceration of the gastric mucosa is a *local* accident in the course of a *systemic* upset, the nature of which upset may be extremely varied. When once damage has been done locally to the wall of the viscus, whatever may be the primary cause, the future course of the process is similar. Pepsin and hydrochloric acid attack the inert gastric cells, necrosis results and ulcer is established. The course, duration and complications of the process depend mainly upon the persistence of the underlying systemic causes, variation in the quality of the gastric juice, local intragastric trauma (as by food, bacteria, etc.) and the influence of the activity of the muscles forming the stomach wall. *Such facts strongly suggest that peptic ulcer presents many aspects of a self-limited ailment.* The role of the physician lies chiefly in the management of the acute or chronic accidents and complications consequent upon the destructive action of the primary cause interacting with the capacity of tissue to protect and repair itself.

From the inception of symptoms, it is impossible to predict clinically the future course of any peptic ulcer. While many ulcers associated with a transiently acting causative agent destroy relatively little gastric mucosa and produce harmless scarification, thus evidencing a tendency to spontaneous cure, other ulcers, seemingly equally innocuous clinically at first, progress rapidly through various pathological stages and in a short time are associated with stenosis, extensive callous formation, hemorrhage, perforation or malignancy. Chronicity in the histo-pathological sense by no means indicates that a peptic ulcer is old in terms of months or years. Malignant changes in gastric ulcer edges may occur quickly and their presence in no way points to the long existence of a previously benign affection.

It is significant to observe variation in the pathological type of ulcers, dependent on their situation in various parts of the stomach. While fully 85 per cent of all gastric ulcers occur in the pylorus,

antrum and along the distal four-fifths of the lesser curvature, and while in these positions the greatest damage can be done by ulcer, yet just as striking changes occur in ulcers situated in other portions of the viscera. It is of importance to note that fully two-thirds of the gastric ulcers occur in that portion of the stomach, the mucous membrane of which is not devoted to the elaboration and secretion of hydrochloric acid, and that duodenal ulcers lie in a mucosa devoted to secreting an alkaline juice, but subjected to vigorous motion and to traumata, physical and chemical, from chyme. It would also seem to be of significance to recall that the majority of peptic ulcers occur in that part of the gut in which the greatest circulatory, muscular and neurological activity is requisite, that the fewest ulcers occur in those parts which are relatively fixed, and which have to perform mainly the duties of food receptacles or of a pepsin-secreting tubular gland.

Physiology. (*a*) *Gastric Chemistry.* It is a striking commentary upon the empirical nature of standard treatments of peptic ulcer that they have as their basis the principle that gastric chemistry has been previously upset. It has been supposed that this disarrangement has been caused either by the development of ulcer or that the upset itself has produced the ulcer. This chemical disturbance is generally put down as being in the nature of an overproduction of acid gastric juice and pepsin. It is presumed that the so-called "corrosive effects" of this overactive digestive juice produces gastric ulcer or prevents healing of one already present. It is significant to observe in the first place that the normal gastric juice frequently varies in strength well beyond the range of the so-called increases, which may be demonstrated when gastric ulcer exists. In a recent study of 500 cases of gastric ulcer in but 30 per cent did I find free HCl values above 0.25 per cent. In 45 per cent the acidity was well within the normal range, and in the remaining 25 per cent the acidity was reduced or was entirely absent. Similar observations have been recorded by other clinicians. That there are causes of gastric ulcer other than the variation in the hydrochloric-acid concentrations is also supported by the observation that in bile-free stomachs large amounts of hydrochloric acid in the concentration of higher than 0.6 per cent mixed with pepsin may be placed in the stomach and yet not produce ulcer. Clinical and histo-pathological evidence indicate that when once initial damage to the gastric lining has been brought about, from no matter what cause, digestion of partly devitalized or necrotic mucous membrane may occur with equal readiness in the presence of normal or even subnormal gastric acidity. Whenever there exists the triad—dead protein, hydrochloric acid, pepsin—the process of local, tissue digestion may go on. It is also quite likely that frequently HCl and pepsin may be absent and destruction of devitalized gastric or duodenal mucosa follow from the

ereptic activity of bacteria in the wall of the gut (primarily or secondarily implanted there systemically or from the lumen of the viscus) or from erepsins present in reflux pancreatic juice.

With these facts in mind it seems strange that treatment of gastric ulcer has largely rested upon a chemical foundation, which chemical foundation is unstable and shifting. Without responsible scientific data, it has been presumed that in ulcer stomachs overacidity was present, and that this overacidity must be counteracted by alkalinization before healing could take place. It has been presumed that the pain of gastric ulcer existed as a consequence of irritation and corrosion of raw mucous surfaces, by gastric juice rich in hydrochloric acid and pepsin, even though the researches of Pawlow, Rehfuss, Carlson, Hertz, Hamburger and others have demonstrated that pain is not commonly present when gastric acidity is highest and that, in known ulcer cases, the introduction of high percentages of acid fails to produce pain. The relief from pain in gastric-ulcer cases is quite as prompt when alkalies are administered in low acid cases, as when such are used in high acid cases. Prompt relief of pain in such instances is also secured by the exhibition of non-alkaline agents, *e. g.*, lavage, antispasmodics, alcohol, opiates, diet, etc. It would seem, therefore, that treatment of peptic ulcer based upon chemical upsets supposed to be associated with the ailment presents much that is empirical and without scientific foundation.

(*b*) *Gastric Motility.* Modern physiological investigations have been especially rich in elucidating the motor activity of the stomach under normal and pathological conditions. Investigators have established the significance of certain gastric cycles of motor activity. They have shown that normally these cycles occur with almost mathematical precision. It would seem that the mechanical factors concerned with digestion are of greater importance than are variations in the secretory function.

The fasting stomach is in a state of tonic contraction. It is rarely empty. Its contents consist of both hydrochloric acid and pepsin. These secretions aid in preserving gastric tone, in digesting mucus, dead bacteria and desquamated cell detritus. Normal hunger is manifested by rhythmic gastric contractions. These seem to precede appetite desire and cause a "want" that leads to eating. Repeated swallowing motions cause certain inhibitions of gastric tonus. Eating accelerates gastric-juice secretion and rhythmic gastric contractions. These peristaltic movements continue so long as food remains in the stomach. They pass from the *pars media* toward the pylorus in regular sequence, thus maintaining a constant pressure in the antrum. Abnormal increases in intragastric tension are prevented by variation in the rate and intensity of the peristaltic contractions and by the rhythmic, interdependent systoles and diastoles of the cardiac and the pyloric

sphincters. The proximal third of the stomach acts mainly as a sac or reservoir and is comparatively free from peristaltic activity. The discharge of chyme from the stomach is intermittent. Seemingly, the pylorus is in some way dependent upon variations in intragastric tension coupled with gastric acid concentration. The presence of acid chyme in the alkaline duodenum may have an influence upon the movements of the pylorus. Acid chyme stimulates the flow of pancreatic juice and bile. It has been advanced that the period of time necessary for these alkaline fluids to neutralize the acid chyme delivered to their reservoir of flow (duodenum) had a local influence with respect determining the duration of pyloric sphincter systole. However, this observation, first made by W. Cannon, has not been fully verified. The alternate opening and shutting of the pylorus with discharge of chyme is continued until the stomach is empty.

(*c*) *Influence of the Kind of Food Ingested upon Gastric Secretion and Gastric Emptying Time.* Water and normal salt solution cause limited gastric secretion and rapid stomach emptying. Their exit arouses but feeble peristalsis. Carbohydrate foods leave the stomach quickly on account of their failure to unite with acid gastric juice. Marked retardation in the discharge of carbohydrates, however, occurs if such be mixed with *alkaline* solutions. The alkali delays the normal feeding-acidity of the stomach and probably permits prolongation of salivary digestion in the stomach. What effect such introduction of an abnormal chemic reaction into the stomach chamber has upon gastric peristalsis has not been explained. Protein food leaves the stomach more slowly than do carbohydrates because proteins combine with free HCl, secondary digestion products develop, and if protein be fed in excess seemingly gastric motor activity is outweighed by the excess secretory activity demanded. Protein has also been shown by Khingine to cause the secretion of 50 per cent more gastric juice during the first four hours of digestion than when carbohydrate is fed. The *pyloric spasm* resulting may then not be in the nature of a true spasm, but merely the evidences of an abnormally prolonged, but not necessarily intense pyloric systole. However, such prolonged systole of the pyloric sphincter may be responsible for a pathological increase in intragastric tension; not infrequently an accompaniment of this is regurgitation of gastric contents into the esophagus, whose cardiac sphincter has been thrown out of normal rhythm by the prolonged pyloric closure. Clinically, this is manifested as "water brash," "sour stomach," pyrosis or even vomiting. Cannon states that at the end of a half hour eight times as much carbohydrate as protein has passed from the normal stomach and that there exists twice as much carbohydrate as protein in the jejunum. While normally carbohydrates begin to leave the stomach at once after feeding, proteins remain from one to three

hours. Fats tarry longest in the stomach; they excite little free HCl productions and excess fat feeding appears likewise to arouse but feeble gastric peristalsis.

Vigorous mixing of food with acid chyme occurs in the antrum and the pylorus, the zone in which 60 per cent of all gastric ulcers are found. Food delay in this locality permits of increased local movement of the viscus, greater opportunity for food and acid to remain in intimate contact with injured gastric lining: hence, opportunity for the maximum of trauma, infection, digestion of damaged tissue, stress on the pyloric sphincter and local alterations in circulatory and neuromuscular mechanism.

The facts enumerated above would appear to have been established as constants by repeated laboratory and clinical investigation. In my opinion they furnish a logical ground-work for the treatment of peptic ulcer. At least, as these observations place such treatment upon the only rational basis which we at present know of; their application is an attempt to eliminate many purely empirical and "rule-of-thumb" features, such as characterize commonly accepted modes of therapy. I am convinced of the practicability and usefulness of their clinical application after eleven years of careful observation.

Diagnosis. In order to insure anything like satisfactory results from measures directed toward the relief or cure of peptic ulcer, it is quite necessary that, before special forms of treatment are instituted, one should have definite proof that ulcer actually exists. This may seem a very trite truism, but is fully warranted and cannot be stated too frequently or too emphatically. In going about the country and mingling with men engaged in hospital or in private practice, I am quite ready to agree with Deaver, who states that not one-half of the patients who are being non-surgically treated for ulcer of the stomach actually have such ulcer, and with W. J. Mayo, who, in opening a discussion on the surgical treatment of ulcer some years ago in the late John B. Murphy's Clinic, began with the statement, "First catch your ulcer." Mistakes in diagnosis of peptic ulcer occur most frequently in clinics or practices where the diagnosis depends chiefly upon history and physical examinations made in accordance with principles laid down by authors who wrote text-books sixty to seventy years ago, or by those modern parrot-scribes who have revamped the old material and turned it loose without experienced scrutiny.

Fully 5 per cent of peptic ulcers give rise to no symptomatology whatever. These ulcers are happened upon during abdominal exploration at laparotomy. In fact, peptic ulcer clinically does not of itself give rise to characteristic symptoms and signs, unless it is associated with such accidents or complications as protected or unprotected perforation, gross hemorrhage, pyloric or cardiac obstruction, etc. Such clinical symptoms as are commonly asso-

ciated with the presence of peptic ulcer to the general medical mind, namely, epigastric pain or distress, pain occurring at the height or after the height of digestion (which pain is usually relieved by taking food), "water brash," pyrosis, so-called sour stomach, heartburn, nausea or vomiting, are but happenings dependent upon certain motor disturbances in gastric physiology. Briefly, these clinical symptoms follow anything which produces local or general gastric spasms accompanied by increased intragastric tension. It thus follows that the symptomatology of peptic ulcer is common to such other abdominal ailments as may produce disturbances in gastric motility. Consequently, many individuals who are affected with chronic appendicitis, chronic infections of the biliary tract, inflammatory lesions of the bowel or of the gastric walls, may experience the clinical syndrome above mentioned. The reason why any so-called diagnostic clinical symptomatology can be attached to real peptic ulcer is that peptic ulcer histologically is in the great majority of instances an intermittently active pathological process. It follows, then, that, in the periods of activity, patients exhibit symptoms dependent upon pyloric and gastric spasms with increased intragastric tension, but that the spontaneous or other type of healing of the ulcer is succeeded by a symptom-free interval when the gastric motor function returns to normal. In the attacks, the gastric motor-spasm syndrome and its associated symptomatology are quite similar in kind to a similar motor-spasm syndrome produced by pathological lesions outside of the duodenum and the stomach (particularly those located in the biliary tract and appendix zones), but with ulcer the symptoms are quite likely to be of aggravated degree. The "gastric motor-spasm syndrome" initiated by extraduodenal or extragastric lesions is not likely to be so characteristically intermittent in its course as is that associated with peptic ulcer. This, itself, is of great diagnostic importance. In fact, to the experienced the chief lesson learned from taking a careful history from patients suspected of peptic ulcer is that of discovering an ailment giving rise to intense disturbance in gastric function at intervals—not as a rule continuously—and that, between these "attacks" the patient is well and happy. If one definitely proves this in the anemnesis he has attained the most valuable single diagnostic fact possible to secure from the history.

Pseudoulcerous dyspepsias commonly occur in young adults affected with biliary-tract or appendix disease. Such ailments are rarely associated in the young with true peptic ulcer, but are very commonly indeed diagnosed as peptic ulcer and treated as peptic ulcer over long periods of time. They furnish that great mass of so-called "acute" or "non-deforming" peptic ulcers, found in the majority of clinics where non-surgical treatments are in vogue or where any widely preached procedure is considered a special feature of such clinics.

True peptic ulcer has proved, in our experience, to be uncommon in individuals of either sex below the age of thirty. The gastric motor-spasm syndrome, so commonly mistaken for ulcer in these young adults, is dependent upon lesions of the appendix zone or the biliary tract in 80 out of 100 patients where it is manifested. This we have proved by carefully following through 2200 patients with the gastric motor-spasm syndrome and below the age of thirty years. We have been so seriously impressed with the significance of our observations and with the folly of attempted non-surgical relief of this type of dyspepsia in the young, that, in individuals under the age of thirty years, who exhibit what the text-books call "acute" ulcer symptoms, unless these symptoms have been accompanied by gross hemorrhage or by perforative gastric or duodenal signs, we have refused to make an unqualified diagnosis of peptic ulcer. This is an important observation, when it is remembered that the group about which we are speaking furnishes the great bulk of "ulcers" being non-surgically treated in the various special clinics or in general practice.

The *abdominal examination* in a peptic ulcer uncomplicated by gastric obstruction or deformity or by perforation returns no significant information. Many of the so-called characteristic local areas of epigastric tenderness are zones of muscle spasm due entirely to extragastric or extraduodenal disease. I am convinced that very frequently, indeed, when doctors point out characteristic areas of abdominal tenderness, such tenderness, as is elicited, is due to pressure upon the spinal nerve roots. Similar areas of tenderness can be readily demonstrated on the other side of the midline.

The *gastric test-meal* furnishes no pathognomonic information. We must get out of our heads and the text-books the idea that increase in gastric acidity means ulcer and that decrease in gastric acidity means that ulcer is healed or is absent. There are too many variations in the normal degree and rate of secretion of gastric juice ever to permit the statement that in any individual the finding of high HCl values is due to or indicative of ulcer.

Our records show that approximately 30 per cent of proved ulcer cases were associated with what might be termed increase in hydrochloric acid values; that the majority of patients had acid within the so-called normal range, while 25 per cent had no free HCl acid or the acid secretion was very low; yet, with all these variations in acidity, in the great group of patients there was no associated variation in clinical symptomatology or in the rate of ulcer progression or of healing.

Test-meal Blood—Occult or Gross. Similarly, the finding of blood in a gastric test-meal or the failure to find it does not mean that ulcer exists or that ulcer is absent. If there is a large ulcer accompanied by much epithelial erosion, then the finding of blood

indicates that an ulcer which is present is, at that particular time of examination, active. Thus, one can appreciate the significance of our own records: Gross or occult blood was present in rather less than 40 per cent of gastric contents and detected in about 33 per cent of the stools. We have never found that such tests as the Einhorn string test and other clinical playthings proved in any way useful in accurately detecting the presence of or of locating peptic ulcer. Many of the blood stains upon these swallowed strings undoubtedly result from the wet string cutting the mucous membrane of the stomach at points of constriction and do not indicate real peptic ulcer. In more than 300 "string" observations upon proved ulcers we had a scant dozen blood stains which might have been liberally interpreted as points of contact with the bleeding ulcer surfaces.

The capacity for gastric emptying is not infrequently interfered with where ulcers occur near the pylorus, either on the gastric or the duodenal side. If a patient takes a full dinner and *persistently* has retention in his stomach upon lavage eight to twelve hours following the ingestion of that dinner, then it may be considered that there is a mechanical defect—a definite reason why the stomach cannot have its contents negotiate the narrowed passageway. In chronic ulcer more than 41 per cent of patients with gastric ulcer exhibit persistent eight to twelve-hour retention, and more than 60 per cent of duodenal ulcer exhibit a similar retention. In 1911, I published these facts, and also showed how important it is in suspected ulcer patients to examine the fasting stomach eight to twelve hours after the administration of a full dinner. Since then emphasis upon this procedure has been made by Straus and Hansman and very recently by Gaither, of Baltimore. I consider that the information derived from thus testing the emptying power of the stomach under the stimulus of a full meal furnishes the chief excuse for giving patients test-meals at all.

The *roentgen-ray* has been of great service in aiding us to recognize whether ulcers are in the stomach or in the duodenum and to give us an idea with respect to the degree of damage which real ulcers have brought about in the gastric and duodenal walls and to adjacent viscera. The roentgen-ray has also led to a complete revision of our statistics as to where peptic ulcers occur and to the relative frequency of incidence of ulcers in the duodenum and in the stomach. Certainly, practically all of our statistics on this point, gathered and published previous to twelve years ago, are valueless and should be consigned to the waste-basket. The roentgen-ray has enabled us to show preoperatively about 50 per cent of true gastric ulcers and between 60 and 70 per cent of duodenal ulcers. I am quite aware that higher percentages are claimed by some roentgenologists, but when one checks up their reports he is quite apt to find that diagnoses unqualified by "prob-

able" or "possible" ulcer rarely reach higher than the above figures. The roentgen-ray is our most useful single diagnostic agent, not only in the recognition of ulcer but also for determining the damage which ulcer has produced. It is our custom to lay great emphasis upon the roentgen-ray showing evidences of gastric deformity, orificial obstruction, displacement and fixation of organs and the like. We consider that when the roentgen-ray shows persistent, local, gastric or duodenal malformation there is little hope of the patient receiving permanent benefit from non-surgical therapeutic procedures. This is so because not only have we then to deal with a lesion which, if it be in the stomach, is a potential cancer, a lesion which may be complicated even when the patient is symptom-free by fatal hemorrhage or perforation, but because scar tissue production deforms the stomach and seriously interferes with emptying time and normal secretory function.

Treatment. Keeping in mind the conception that peptic ulcer is rarely a primary gastric or duodenal fault, but is usually a secondary happening in the course of an acute systemic or chronic constitutional disturbances, it becomes evident that if one is to rationally attempt relief or cure of peptic ulcer he must recognize the primary etiological fault and attempt its eradication or its alleviation. It follows then that one must as energetically treat the patient who harbors the ulcer as he does the ulcer in that patient. If this be the plan of action, provided one has not to deal with such acute accidents as hemorrhage or perforation or such chronic complications as stenosis, visceral deformity and fixation, malignant degeneration, etc., the peptic ulcer will heal after Nature's fashion if too much interfering effort is not applied, intragastrically and intraduodenally.

(*a*) Selection of Cases for Types of Treatment. As I have said, recognition of the primary systemic fault is often difficult. Inasmuch as foci of infection may exist in oral adenoid tissue, head sinuses, about teeth or in systemic lymph-gland chains, these must be removed promptly. Intra-abdominal infections must likewise be eradicated, *e. g.*, diseased appendix, gall-bladder, Fallopian tubes, ovaries, ulcers or subinfections of the bowel. It would appear quite inadequate to remove external, local foci of infection and to leave behind intra-abdominal foci containing bacteria already accustomed to their environment and ready to spread their operations to the gastric or duodenal lining when opportunity offers. It would appear that the removal of these variously situated germ centers constitutes a fundamental step toward the cure of many gastric ulcers. Careful general scrutiny of the patient for cardiac leakages, myocardial insufficiency, capillary sclerosis, anemia, evidence of occupational poisoning, endocrine malfunction, improper environment, overwork or nervous stress must be made. These are all causes leading to or aggravat-

ing ulcers. If their importance is minimized, then advantage of aid from the constitutional side of the individual is lost and ulcer healing certainly delayed. At least two negative Wassermann tests should be recorded before any treatment which excludes antiluetic therapy is decided upon. It is quite surprising how frequently a positive Wassermann test, even though a history of lues cannot be obtained, will aid in the exhibition of remedies and accelerate ulcer *cure*.

After local foci of infection have been removed the mode of treatment is further influenced by the type of ulcer that has been proved to exist. Unless ulcers complicated by much scarring or causing great gastric deformity are demonstrated to be luetic, little hope of permanent relief by medical regimens can be offered. Surgery promises the greatest prospect of relief to such cases. Intense pain, frequent hemorrhage, perforation or the danger of malignant change taking place in calloused ulcers likewise contraindicate non-operative care. Unfortunately we have no clinical or laboratory tests which indicate to us what type of gastric ulcers will become malignant or when early malignant change is taking place. However, we can be consoled by knowing that malignancy in connection with duodenal ulcer is rare. The roentgen demonstration of calloused gastric ulcer exceeding 2 cm. diameter, when such is associated with history of frequently recurring ulcer symptoms and the positive chemical test for blood constantly determined in the stools, forms a clinical hint that malignancy can be expected. The most competent clinicians are agreed that calloused recurring ulcers located in the pyloric end of the stomach should be treated operatively. Excision should be performed when mechanically possible. If excision is impractical then infolding or cautery puncture, with or without gastrojejunostomy, yields the most satisfactory results. In non-obstructing ulcers it would seem that gastrojejunostomy should always be accompanied by permanent pyloric closure if one is to secure a perfect and permanently emptying stoma. Gastrojejunostomy, properly performed, acts by aiding gastric emptying, by decreasing intragastric tension, by, at least temporarily, diminishing free HCl (an average of 20.5 points in 273 consecutive cases in our series) and by permitting limited alkaline jejunal regurgitation into the stomach.

Thus, successful non-surgical treatment of ulcer first demands careful selection of cases to be so treated. It is indicated only in ulcers associated with little callus, or if calloused, located in portions of the stomach in which stenoses are not liable to result, or where surgical procedures cannot be carried out. Certain essential principles brought out by our review of the ulcer problem given above must be borne in mind in carrying out medical treatment.

(*b*) Principles Underlying Treatment. The most useful features of what I have suggested with respect to the non-surgical management of peptic ulcer are:

1. The recognition that such ulcer is not a primary gastric ailment; treating it as such without bearing in mind its systemic or constitutional origin offers little hope of permanent improvement.

2. Recognition of the type of ulcer at hand (from the etiological as well as the histological viewpoints) is absolutely essential before any method of therapy can be rationally directed.

3. Gastric chemistry plays a comparatively insignificant role both in ulcer production and in delay in ulcer healing. Ulcer dyspepsia is largely the manifestation of abnormal gastric spasms, disarrangement of normal gastric peristalsis and an excessively increased intragastric tension.

4. The principle underlying all local treatment of the gastric fault is the fundamental one of giving the injured part *physiological* rest and then not interfering with the natural tendency to heal inherent to all body tissue. *By adopting this principle of physiological rest to the affected part, it will be recognized that I have brought into the non-surgical therapeutic regimen of peptic ulcer those essential principles for healing which our surgical colleagues have so effectually proved necessary to the repair of any traumata whether by incision or from extraneous agents.* Whether the surgeon has to deal with an abdominal wall cut or a varicose ulcer of the leg, he finds that most rapid and permanent healing follows rest by fixation, suitable posture, favorable temperature, cleanliness and the avoidance of traumata from movement, antiseptics or so-called "healing" lotions, pastes and powders.

In actual practice physiological rest and repair of tissues harboring gastric ulcers are obtained in my clinic by the following regimen:

(*c*) Outline of a Method of Non-surgical Management. 1. *Rest in Bed.* Physical and mental rest for from one to three weeks; bodily and psychic activity alike are capable of stimulating peristalsis.

2. *Physiological Rest to the Affected Part* (*Stomach*). Complete rest demands avoidance of food, *per orem*, irritating medicine, gastric lavage and frequent abdominal examinations of the suspected focus.

3. *Local Applications to the Abdomen.* Painful spasms are prevented by having constantly applied to the abdomen compresses saturated with a hot solution of alcohol and boracic acid. These compresses may be kept heated by an electric pad or partly filled water bag and should be worn day and night without interruption.

4. *Keeping the Stomach Empty of Food.* This promotes healing by limiting local irritation from the food itself, by reducing the amount of gastric juice required to digest food, by limiting gastric peristalsis and by avoiding painful gastric spasms, which last tend to prevent free circulatory interchange at the ulcer-bearing area. Abstinence from food by mouth should be insisted upon for from

three to seven days, according to the type of patient under care. The period of fast is determined best by the clinical disappearance of gastric spasm (pain, regurgitation, "water brash," "heartburn") and by fluoroscopical proof of absent or diminished gastric peristalsis. During the fasting period, paraffin wax is chewed for ten minutes every hour. The wax mechanically keeps the mouth clean, promotes free flow of protective saliva and mucus, prevents parotitis, aids in counteracting the development of painful hunger contractions and gastric spasm, local and general, and allays thirst.

5. *Rectal Feeding.* During the fasting period rectal feedings are instituted. From 300 to 600 calories of nutrient mixture are given each twenty-four hours in approximately 1000 cc of normal salt solution. I use a clyster containing 1 ounce of 50 per cent alcohol, 1 ounce of glucose, and normal salt solution to make 240 cc. The nutrient enema is given at body temperature by the drop method. The drops flow at the rate of 30 to 60 drops a minute and at least four such clysters are given in twenty-four hours. Should the patient be in great pain or affected with pronounced gastric irritability during the first day of rectal feeding, tincture of opium or tincture of belladonna (10 drops), or both, are given in each nutrient enema.

6. *Mouth Feeding.* When mouth feeding is begun (usually from the third to fifth day) two principles control the basis of diet: (1) Nourishment should be liquid and administered warm in small quantities, and these given frequently, and (2) carbohydrates should be selected.

(*a*) Small quantities of liquid food should be frequently administered in order that the stomach may empty rapidly, with the least effort on its part and thus it may remain food-free for the longest time. This procedure makes available the maximum time for rest at an ulcer site. Jejunal digestion must be called upon until gastric conditions warrant functional activity by the stomach. A fasting, food-free stomach contains hydrochloric acid or pepsin at a minimum. When the feeding *per os* is begun, from 2 to 4 ounces of warm liquid nourishment are given each waking hour. When gastric irritability is very pronounced and the patient is in great need of food, carbohydrate mixtures may be given intermittently or constantly with the aid of a duodenal tube, constantly *in situ*.

(*b*) As experimental facts have established, of all basic foods, carbohydrates leave the stomach most quickly and give rise to the minimum amount of functional activity. Therefore, liquid carbohydrate mixtures (barley water, rice gruel, thin cream of wheat, dextri-maltose, ovaltine, malted milk, thin creamed vegetable soup, etc.) are allowed. *Milk is not given as routine.* Milk results in almost pure protein clots in the stomach during its prepar-

atory stages of digestion. In the stomach these clots act precisely as do other proteins: they remain for a long time, act as sources of irritation, as stimuli to acid and pepsin secretion and furnish choice culture media for bacteria. If milk be given at all it should be first parboiled, citrated or predigested. If the gastric contents are low in acid and their bulk is carbohydrate, slight demands are made upon the stomach as regards either secretory or motor activity. The pylorus thus remains free from prolonged systoles and quick gastric emptying follows. By this means, the stomach avoids gastric stagnation and the intragastric accumulation of relatively high free and combined acids; particularly their accumulation in a viscus whose *tonus* or *tension* is apt to be greater than normal. This free gastric emptying prevents the development of hypernormal peristalsis, the influence of which factor is potent in the prevention of physiological rest (secretory and motor) to the ulcer area. It also renders unnecessary frequent, disturbing, gastric lavage or the exhibition of hugh quantities of alkaline drugs.

7. *Limitation of the Overproduction or Overaccumulation of Free Gastric Acid.* This is obtained by keeping the stomach food-free as above described. The ordinary stomach secretes very little HCl and pepsin after a forty-eight-hour fast; its peristaltic activity is held in abeyance or very feeble after this interval. The stomach is then in a state as ideal as possible for epithelialization at the ulcer site.

If the above points, as established by modern physiological research, are borne in mind, the exhibition of large quantities of alkali or other medicines is unnecessary. Many of our patients receive no medicines whatever by mouth. Pain, vomiting, regurgitation and pyrosis quickly disappear. Healing is accelerated and duration of hospital residence is shortened. Providing the gastric lumen is patent, the stomach empties freely; there is no stagnant, irritating residue requiring frequent lavage in order to insure the subject's comfort. Large quantities of alkali, according to Pawlow and to our clinical and laboratory experience, create pernicious increases of gastric acid and of mucus. Relief by lavage is then demanded. It would seem an absurd and contradictory clinical procedure to exhibit alkalies and thus create an intragastric state which then calls for removal of the accumulated foreign mass in order to insure a patient's comfort. It is true, that often large quantities of alkali bring about relief of symptoms, but mere symptomatic quiescence in no way indicates healing of gastric ulcer. The stomach has a remarkable capacity for neutralizing huge doses of alkali if it is compelled to do so, but there is no physiological reason why it should be called upon thus to overwork, when, physiologically, secretory activity may be controlled by fasting and later by diet. It will be remembered that the normal

habitat of gastric epithelium is an acid or, at the best, a neutral medium. If such epithelium is made to live in the presence of excess alkali, it lives under the handicap of an environment foreign to it constitutionally. Experiments in artificial tissue growth have shown that cell proliferation is retarded by hypertonic alkaline quite as well as by high acid solutions. Hence, overalkalinization may actually prevent healing. Attempts at protection from this foreign body (excess alkali) are shown: (1) By the acid-producing glands oversecreting; (2) by the mucoid degeneration of physiological fatigue, which results in the throwing out over the secretory glands of a protective layer of mucus; and (3) by delay in repair. Excess or continuous exhibition of alkali results in enormous secretion of acid and mucus; this is at least a partial explanation of the so-called "hypersecretion" associated with gastric ulcers, particularly when such are treated by the continuous alkalinization method first proposed by Leube, and frequently since then resurrected under a score of names. To combat the state of affairs subsequent to alkaline exhibition, the patient's stomach must of necessity be washed frequently or increasingly greater quantities of alkali must be given to overwhelm the stomach's defensive mechanism; then there follows physiological fatigue or exhaustion of the acid-secretion mechanism. It is a common observation that such patients as are treated for ulcer by the overalkalinization procedure always require frequent gastric lavage to insure their comfort. This frequent lavage is to be condemned not alone because it acts contrary to the fundamental principle requisite for healing, namely, rest of the affected part, but also because it creates distress in patients already undernourished, nervously and physically wearied, may be the cause of serious accidents and, moreover, is an unwarranted procedure scientifically. To those who, fluoroscopically, have watched the behavior of a stomach during lavage it is self-evident that the maneuvre defeats this primary principle of healing. Commonly, lavage is accompanied by vigorous gastric contractions; these persist not only during the procedure, but frequently persist for an appreciable time afterward. If dieting and general management are planned as above outlined lavage is not demanded for comfort. In the past eleven years I have not employed lavage therapeutically in ulcer cases more than a dozen times. Lavage is so rare a procedure in my clinic that my associates and patients consider it as almost contraindicated. It can be readily judged how a treatment, of which lavage does not form a prominent feature, contributes much to a patient's peace of mind and shortens the period of hospital incarceration.

Recent reports from the Mayo Clinic and from other institutions, where the treatment of true peptic ulcer by the continuous overalkalinization method has been tried, indicate that certain

patients to whom large quantities of alkali are given develop severe toxic symptoms. Even when large doses of alkali have been administered, gastric acidity is not noticeably or permanently reduced. Moreover, many of these patients develop toxic symptoms, as dizziness, headache, nausea and vomiting. That this is really a toxemia, the consequence of administrating excess alkali, may be proved by study of the blood chemistry. Hardt reports that under alkaline ulcer regimen the blood urea may increase six times, blood carbonates practically doubled and creatinin increase more than 100 per cent. Of 30 patients thus treated in Hardt's department at the Mayo Clinic, fully one-third developed symptoms of toxicity as shown clinically and by study of the blood chemistry. Some of these toxic patients exhibited definite tetany. This phase has been commented upon recently by Tisdall, of the University of Toronto. He has shown that these toxic reactions result from increase of the bicarbonate ion of the blood, while there is no evidence of disturbance in calcium-phosphorus ratio of the blood. MacCallum and his co-workers have reported similar blood changes. Old, feeble patients, the subjects of arteriosclerosis, are especially likely to exhibit toxic evidences of overalkalinization; but these do not exclusively form the group so affected.

8. *Administration of Medicines.* It is doubtful if any kind of medicine has a direct healing effect upon peptic ulcer. In our service medicines are administered largely to counteract discomfort due to three main causes, namely: (1) Painful gastrospasms; (2) accumulations of overacid gastric contents associated with peristaltic unrest; (3) pain associated with perforation or ulcer progression.

(*a*) *Painful Gastrospasms.* These are usually controlled by carrying out the dietetic principles which I have above outlined. The chewing of paraffin wax relaxes the pyloric spasm largely through stimulating a proper swallowing reflex and by fatigue of hunger-like contractions. Certain types of case in which there is an individual vagus hypertonia, or where ulcers are located at or near the orifices, demand the exhibition of antispasmodic medicines, such as atropine, tincture of belladonna, or bromides. In the early stages of the treatment, when the stomach is being kept as free as possible of contents, atropine may be given hypodermically or tincture of belladonna or bromides may be dissolved in the nutrient enemata. Later, when food is being given by mouth, tincture of belladonna, in doses of from 5 to 15 drops, may be administered fifteen minutes before feeding and as frequently as three to six times daily. We have not found useful, as analgesics, large doses of such so-called "protective" medicines as bismuth and olive oil. These medicines doubtless act by affecting the rate and intensity of peristalsis, although they may have some effect in certain cases by direct action upon the ulcer. At times

orthoform, given in 10 grain doses, in warm water, is an efficient local anesthetic, when it is able to come in direct contact with an open ulcer.

(*b*) *Relief of Overacid Gastric Accumulations.* For this purpose sodium bicarbonate is contraindicated, since its administration results in the production of annoying accumulations of carbon dioxide with resultant gastric retention or painful belching, and because its neutralizing value is comparatively low. Large quantities of bicarbonate of sodium are necessary to give relief, and the administration of such, secondarily, produces excessive gastric secretion. Toxic signs most commonly follow the exhibition of huge doses of the carbonates of soda. If alkalies are indicated better results are obtained by the exhibition of frequent small doses of a fluid form, as milk of magnesia or solutions of calcined magnesia. When alkalies are used the ordinary patient is very comfortable when from 5 to 10 grains of calcined magnesia are given every two or three hours. Many cases require no exhibition of alkali if the physiological principles above outlined form the basis of the treatment. As I have mentioned, only on very rare occasions is it necessary to employ gastric lavage. When it is employed warm Carlsbad water (1 dram of artificial Carlsbad salts to 1 quart of water) may be satisfactorily used.

(*c*) *The Acute Prostrating Pains of Perforation of Ulcer Extension.* These are best controlled by the administration of morphine hypodermically, rest in bed and hot compresses to the abdomen. Prompt and skilled surgery offer the patient the greatest hope for relief in such crises.

9. *Hemorrhage.* Constant seepage, demonstrated either microscopically or clinically, is an indication for early abdominal section. Intermittent seepage may be controlled best by rest in bed, morphine hypodermically, intravenous injections of fresh horse serum or by copious transfusion of whole blood after the methods suggested by Kimpton and by Percy. In acute hemorrhage, accompanied by vomiting, prompt lavage of the stomach with water at 100° F. frequently stops both the vomiting and the hemorrhage. The exhibition of morphine, rest in bed and whole blood transfusions generally prevent recurrence of hemorrhage. In this class of case, however, surgical intervention should be resorted to early, and this especially if, in a given patient, frequent, copious, prostrating hemorrhages occur.

10. *Bowels.* During the early period of treatment simple soapsuds enemata may be administered every second day. After the second week, morning doses of phosphate of soda or of Carlsbad salts in hot water may be given. In chronic cases, liquid paraffin given in equal quantities of warm cream result in easy motions, and the paraffin appears to have certain protective value upon the ulcer-bearing area.

11. *Lues.* When it is suspected that lues is an important etiologic factor specific therapy should be vigorously pushed. Ulcer, clinically, of the infectious type may be helped toward healing by autogenous vaccines, the material for cultures being obtained from teeth roots, tonsils, sinuses accessory to the nose or from biliary tract drainage, *per duodenum.*

12. *Anemia.* Anemic patients usually require the exhibition of iron and arsenic in full doses if their tissues generally are to be expected to respond by maximum healing at the local gastric fault. Patients who come to our service greatly undernourished, with dry skin and mucosæ and exhibiting red counts as low as 3,500,000 have their bloods typed, and without loss of time consequent upon attempts to improve the blood by drugs, given spaced transfusions of 600 to 1000 cc of whole blood by means of Percy's modification of the Kimpton-Brown tube. It is remarkable how rapidly even desperate cases progress to healing after these initial constitutional boosts.

Summary. 1. Results of the non-surgical treatment of peptic ulcer have proved unsatisfactory because relief of symptoms and signs has been regarded as indicative of cure of the affection. Follow-up records of peptic ulcer patients demonstrate that symptom subsidence is not necessarily proof that the ailment has been healed permanently. Grave complications may occur when the subject is symptom-free and apparently physically vigorous.

2. The etiology of peptic ulcer is varied: subinfections, circulatory visceral disturbances, lues, neurological or endocrine imbalance, occupational hazard and trauma would appear to be types of anomaly leading to a systemic or constitutional fault, a local gastric manifestation of which takes the form of peptic ulcer. Considered from such viewpoint, gastric ulcer presents features suggestive of its being a self-limited local lesion.

3. There seems to be no evidence that ulcer is caused by alterations in gastric chemism or that its presence or course, fundamentally, are influenced by variations in the HCl-pepsin content of the gastric juice. The clinical symptoms coincident with uncomplicated ulcer are not explainable on the basis of abnormal secretory function; severity of symptoms bears little, if any, relationship to quantitative or qualitative variation in the acidity of gastric juice. "Hyperacidity" does not mean ulcer, nor does ulcer indicate "hyperacidity."

4. When ulcer is not complicated by such pathological phenomena as stenosis, perforation, gross hemorrhage or malignancy, the associated gastric digestive syndrome is most satisfactorily explained by regarding symptoms and signs as indicative of gastric, motor disturbances. The chief factors concerned with such abnormal gastric motor anomalies are: (1) Interference with the normal orderly peristaltic interrelationsip between cardiac and pyloric sphincters,

and (2) between the activity of these sphincters and true gastric peristalsis. The effect of such failure of peristaltic coördination is increase in gastric tone and of intragastric tension.

5. It has been shown that gastric motor function is influenced by the kind of food intake. Carbohydrate demand the least motor or secretory work from the stomach. Such feeding lengthens the interdigestion phase of gastric diastole and secretory rest. The recognition of this physiological phenomenon establishes a fundamental starting place in the institution of a rational regimen for the non-surgical treatment of peptic ulcer.

6. Statistics of the results of gastric ulcer treatment are valueless unless definite proof is adduced that ulcer actually were present during the exhibition of any special regimen. Much of the literature which has been concerned with "ulcer cures" is worthless, because no proof is submitted which establishes that gastric ulcer existed in the patients under treatment. Any intra-abdominal pathological lesion or any systemic disturbances capable of initiating gastric motor incoördination, whether or no such be accompanied by secretory faults, or increased intragastric tension is capable of giving rise to "ulcer-like" symptoms; these require discriminating judgment to separate them from the digestive disturbance concomitant with true peptic ulcer. Ulcer diagnosis rests on a nice balancing of facts returned from clinical history, physical examination and roentgen observation.

7. When ulcer has been proved to exist, success of therapy is strictly dependent upon selection of instances for surgical or non-surgical treatment according to the pathology present. Unless luetic, little hope of non-surgical cure can be held out when ulcers are accompanied by obstruction, gross scar, and lesion of crater type, or have bled freely or exhibit malignancy.

8. A method of non-surgical, clinical management of selected cases is described. It aims, rationally, to take clinical advantage of established gastric physiological principles, especially, should peptic ulcer be accompanied by provable departure from the normal sequence of gastric motor function. It emphasizes, particularly, the necessity for attempting to bring about in the stomach physiological rest: motor and secretory. Thus it brings into the non-surgical clinical regimen of peptic ulcer, the primary principle of healing so thoroughly established surgically as essential for the repair of tissue damage in general. Further, the form of treatment advanced takes into consideration the systemic or constitutional inception of peptic ulcer and disregards the ancient theory of abnormal gastric chemistry being a factor against ulcer repair. Alkalies or other drugs and gastric lavage play a very minor part in the regimen described.

9. The treatment suggested has the advantages of being simple, inexpensive, easily borne and it shortens the period of hospital incarceration. In selected instances it permits unimpeded ulcer healing.

THE REACTION OF THE PARATONSILLAR TISSUES TO TONSILLECTOMY: A STUDY IN THE ETIOLOGY OF POSTTONSILLECTOMY PULMONARY ABSCESS.*

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and

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Introduction. Since the appearance, eleven years ago, of Richardson's[1] paper there has developed, especially in the last few years, a deep interest in the incidence of lung abscess as a sequel to tonsillectomy. A recent comprehensive study of the situation, based on a widely circulated questionnaire, has been made by Moore,[2] who gathered reports of 202 cases. Among his conclusions are the following: "The vast majority of cases are of inspiratory origin because of (*a*) time of development and (*b*) involvement of the lower lobes of the lung in 60 per cent of the cases (right lower, 41 per cent; left lower, 19 per cent), being almost the same relative incidence as in cases of inspired foreign bodies.

"Blood-stream transmission of infected material, causing pulmonary abscess, occurs, but in a relatively small number of cases. Lymphatic extension is a rare mode of infection."

Possible Pathways of Infection. With this dire sequel occurring so frequently, and it cannot be questioned that it happens oftener than even Moore's paper would lead us to think, the thoughts of all interested must turn toward the reason or reasons for its occurrence and the adoption of methods of prevention.

The infection must reach the lung either (*a*) by way of the trachea and bronchi (bronchogenic), (*b*) by way of the venous system (hematogenic) or (*c*) by way of the lymph channel (lymphogenic). The writers of this paper instituted this study with no preconceived theory as to which pathway is the preponderating one, but they were of the opinion that the likelihood of the inhalation method of infection has been taken too much for granted. The fact that in Moore's series of 202 cases 39 (approximately 20 per cent) were secondary to operation under local anesthesia strengthened this view.

Influence of Complete Tonsillectomy upon the Incidence of Lung Abscess. It was in 1912 that attention first was drawn to lung abscess as a sequel to tonsillectomy. And it was about that

* Read at the Forty-fifth Annual Meeting of The American Laryngological Association, held at Atlantic City, N. J., May 16, 17 and 18, 1923, and before the College of Physicians of Philadelphia, December 5, 1923.

time that the so-called "tonsillotomy" was being discarded in favor of complete removal, including the capsule. Possibly this is not a pure coincidence. Dean[3] says, "In my experience the infections have been much more frequent and severe since I have been performing tonsillectomy and not tonsillotomy." The infections he refers to are those in the immediate region of or adjacent to the tonsil. The incomplete tonsil operation, whether performed by guillotine, punch or what not, invariably left behind a mass of tonsil tissue walled off from the throat by a very firm and capable capsule. The raw surface left after operation was composed only of tonsil tissue with its associated vessels. No injury had been inflicted or infection implanted upon the muscle or other deeper structures of the pharynx, and no vessels of the tonsillar and pharyngeal region were traumatized or severed. In those days the use of a general anesthetic was universal and no suction appliance was in use, and yet posttonsillectomy lung complications were neither noted nor reported.

Lung Infection of Bronchogenic Origin. Let us consider for a moment the question of air-route infection. A fair fundamental question would be this: Is the lung very susceptible to infection through the air passages? The answer is, It is quite probable that the lung possesses inherently a highly protective margin of safety. This is evidenced by the fact that many injurious objects, notably bacteria, are daily being inspired under many and varying conditions with no deleterious result. General anesthesia offers a good opportunity for plugs of mucus and clumps of bacteria to enter the respiratory spaces, thousands of cases with dirty mouths are being etherized, but postoperative pneumonia is not as common as the possibilities thus afforded would lead us to anticipate. For example, in Cutler and Hunt's[4] 1920 series of 1604 operations there were but 7 cases of bronchopneumonia and 1 of lobar pneumonia occurring as complications. In these 8 cases local anesthesia was used once (in the lobar pneumonia case), gas-oxygen four times and ether three times.

Moreover, the production of experimental pneumonia by the atomizing of bacteria into the trachea has proved very difficult of attainment. It has succeeded regularly only when very large doses or highly virulent organisms have been used and when they have been introduced by puncturing the trachea through the skin of the neck.

The question might be put more broadly: Are unbroken or even broken mucous membranes reasonably subject to septic invasion? For example, is an abscess of the nasal septum not a very rare condition? How many rhinologists have seen an abscess of a turbinated body, and this even considering the abrasions and open pathways for infection caused by the common habit of finger removal of crusts from the nose? How many cases of foreign

body in the bronchial tree, the esophagus, the eye, the urethra or the intestines are followed by abscess? Very few! Of course, the bronchial and pulmonary mucosa may be less tough than that in the other locations mentioned; but even granting this, when a lung inhales some septic material in which are microörganisms to which the individual is probably partly immune, why should we necessarily assume that this inspired material is the cause of an abscess to the exclusion of other possible sources of infection?

Lung Infection of Hematogenic Origin. On the other hand, postoperative pulmonary embolism, following surgical procedures in the abdomen and elsewhere, is a common condition. Many of these cases are badly shocked and die promptly, because the embolus comes from a large vessel and blocks off a large branch of the pulmonary artery and a large area of lung. Even if the embolus is a septic one, death in such cases usually occurs before an abscess has time to form.

In the field of general surgery the thoughts of investigators are turning decidedly toward the embolic nature of postoperative lung complications. A careful and exhaustive study recently has been made by Cutler and Hunt[5] of a year's cases in the surgical wards of the Peter Bent Brigham Hospital, where a specially careful watch has been kept for the appearance of postoperative lung lesions. As the result of improved methods of case-watching and study, the percentages of such complications found has more than doubled in five years. Along with this naturally has come a drop in mortality percentage, because many small lesions have been discovered, lesions which appeared and disappeared with but few symptoms.

During 1920, 1604 cases were operated upon, and "63 of these patients developed a pulmonary complication that might be attributable to the operative intervention or to the anesthetic. There were 5 deaths among these 63 cases. Thus in 3.93 per cent of the cases (1 in 26) a complication developed and 0.3 per cent (1 in 321) patients died from one of the complications."

In this group of 63 there occurred 1 case of lobar pneumonia, 7 of bronchopneumonia, 16 of bronchitis, 2 of exacerbation of tuberculosis, 2 of pleurisy, 1 of empyema, 32 *of pulmonary infarction* (italics ours) and 2 of pulmonary embolism. Thus, even in a general surgical clinic approximately 1 case in 50 was complicated by an infarction of the lung, which shows that this form of pathological lesion occurs more frequently than is generally thought.

Among their conclusions are the following:

"Irritation and aspiration due to inhalation anesthesia may be the cause of a small percentage of postoperative pulmonary complications.

"The fact that these complications occur with local anesthesia, with inhalation anesthesia in the most expert hands and in a

definite relation to the mobility of the operative field, is taken as evidence against the importance of the irritation of inhalation anesthesia in the production of these lesions."

W. J. Mayo[6] states that septic emboli from the operative field are a common cause of secondary pulmonary complications. He laments that these complications are too frequently attributed to the anesthetic, and says that they are quite as frequently found in cases in which local anesthesia is employed. Many other surgeons could be quoted to the same effect.

Among otolaryngologists the possibility that these lung lesions are of embolic origin is not entirely a new one. Of those who might be quoted in this respect are Richardson, Porter, and Simpson and Noah.

Richardson[7] in his 1912 report describes 2 cases under the title of "Septic Infarct of the Lung."

Porter[8] says: "There exists a complicated network of veins, the plexus tonsillaris and the plexus pharyngeus, which cover the outer walls of the pharynx and the tonsillar cavities, receiving blood from the tonsils, tonsillar pillars and pharyngeal walls. These vessels are exposed and always injured even in the gentlest operative work. This too is a field impossible to protect from germ-laden saliva and pus. It is therefore not difficult to believe that infected emboli could be dislodged from veins thrombotic from trauma and infection, located in an area active in every attempt at speech and swallowing. I feel that there can be no doubt that infected emboli travel direct to the lungs and cause certain cases of pulmonary abscess."

Simpson and Noah[9] state, "The writers believe that aspiration does not account for the production of lung abscess in the 2 cases reported." They conclude: "1. During or following operation septic material enters the veins, passes through the right heart to the lungs and there finds, in the presence of a tuberculous lesion, suitable soil for the production of an abscess.

"2. The possibility of aspiration of infected material as a cause of pulmonary abscess is not to be denied, yet we believe that more cases occur as a result of hematogenous infection than is generally supposed."

Answers to Arguments Favoring Bronchogenic Origin. A common argument in favor of the aspiration of infected matter as a cause of lung abscesses is that in location (preponderatingly on the right side and in the lower lobes) they correspond quite closely to that of foreign bodies. We believe this argument is not as definitive as appears on the surface, for the following reasons:

1. Foreign bodies have no monopoly of localization in the right lung and its lower lobe. Pulmonary emboli, especially massive ones, seek the right side to even a greater degree than do foreign bodies. An abstract[10] of an article by Capelle[11] states that:

"Pulmonary infarction and embolism (*massive*—authors) was stated to have occurred in 15 among 10,000 operations, but many cases called postoperative pneumonia are really instances of small pulmonary infarctions. A distinguishing sign is the bright-colored blood expectorated as compared with the rusty sputa of pneumonia."

Then follows a sentence having marked bearing on the question we are discussing: "Thirteen presented changes in the back and front of the lower pulmonary lobes, and in only 2 were the signs restricted to the left lung." Thirteen out of 15 were in the right lung and all of them in the lower lobe! Does this not cast doubt upon the location of lung abscesses proving their inhalation etiology? So much for *large* emboli.

In searching the literature for data as to the localization of *small* infarcts we were unable to find definite figures. A letter of inquiry to Dr. Elliott C. Cutler[12] brought a generous and prompt response, and we are able to give his unpublished figures on this point. We herewith desire to express our deep appreciation of his kindness. His table is as follows:

DISTRIBUTION OF POSTOPERATIVE PULMONARY INFARCTION.

	1920 cases.	1921 cases.
Right upper lobe	0	2
Right middle lobe	2	1
Right lower lobe	14	7
Left upper lobe	0	0
Left lower lobe	5	4
Both lower lobes	2	1
Right upper and middle lobes	1	0
Left upper and lower lobes	1	0
Totals	25	15

Cutler had accurate data on 40 of his cases. Of these 21 were in the right lower lobe only and 9 were in the left lower lobe only (21 to 9); 30 of the cases involving more than one lobe were located in the right lung and 13 in the left lung (30 to 13).

Welch[13] states that: "The course followed by an embolus in its travels is determined by purely mechanical factors, of which the most important are the size, form and weight of the plug; the direction, volume and energy of the carrying blood stream; the size of branches and the angles at which they are given off, and the position of the body and its members. In accord with these principles we find emboli in the lower lobes of the left lungs oftener than in the upper, and in the right lung oftener than in the left, the right pulmonary artery being larger than the left."

The size of the right pulmonary artery and right lung is to that of the left pulmonary artery and left lung as 4 is to 3. Therefore, an embolus leaving the right heart, other things being equal,

would have 4 chances of going to the right lung to 3 of going to the left, or in 100 cases 57 would go to the right and 43 to the left.

2. Another factor could be the course of the two pulmonary arteries as and after they leave the pulmonary aorta. Possibly the right pulmonary artery is in more direct line with the pulmonary aorta than is the left. We are at present studying this piece of anatomy, but are not yet ready to report.

3. The inhalation of bloody throat secretions during tonsillectomy is, in our belief, not precisely comparable to the dropping or inhaling of a foreign body into a bronchus. In the great majority of cases foreign bodies enter while their host is in an erect posture, and in dropping down the trachea they naturally would tend to enter the wider and more vertical right bronchus. On the other hand, during tonsillectomy, under ether, with the exception of certain parts of New England, the patient usually is in a recumbent position and gravity could have little or no bearing on the problem. Whatever enters the trachea is drawn in during inspiration and consists of frothy, bloody mucus and tonsil crypt contents. It moves up and down the larynx and trachea during respiration, and when a collection of this material reaches the tracheal bifurcation it is almost as likely to be inspired into the left lung as into the right.

4. A final argument against the general acceptance of the respiratory theory of these lesions is the fact that so many are reported as being sequential to operation under local anesthesia.

With these facts in mind it is at least conceivable that the inhalation theory, based upon a wider right bronchus with a more direct course in relation to the trachea, should be relegated to a less important place than it hitherto has occupied in the minds of otolaryngologists.

Reason for and Plan of Present Communication. With these thoughts as a working basis, it occurred to us that a minute study of the pharyngeal and cervical region following tonsillectomy would tell us exactly what happens there as a result of the operation. We hoped that examination of the peritonsillar tissues, and especially of those venous and lymphatic tissues which drain the tonsil area, might afford information as to the probable location of the *fons et origo* of lung abscess. We felt that we would be studying a region into which septic tonsil contents are squeezed during operation, which would be traumatized during operation, into which needle-borne septic sutures frequently are carried during operation and which is wide open to constant microörganismal infection after operation. Such conditions are ideal for the formation of septic thrombi which later could become detached and pass down the internal jugular vein into the right heart and thence into the lung. We felt also that there is hardly any place in the body where thrombi would be more likely to become detached,

because the contraction of the tongue and throat muscles during swallowing certainly would promote the loosening of vein clots and the starting of them on their way down the jugular, through the heart and into the lung.

The present communication is based upon the results obtained from operations upon animals. Our experiments were as follows: One animal we devoted solely to the identification of the tonsil lymph node, using Gerota's technic, as employed by Wood[14] in

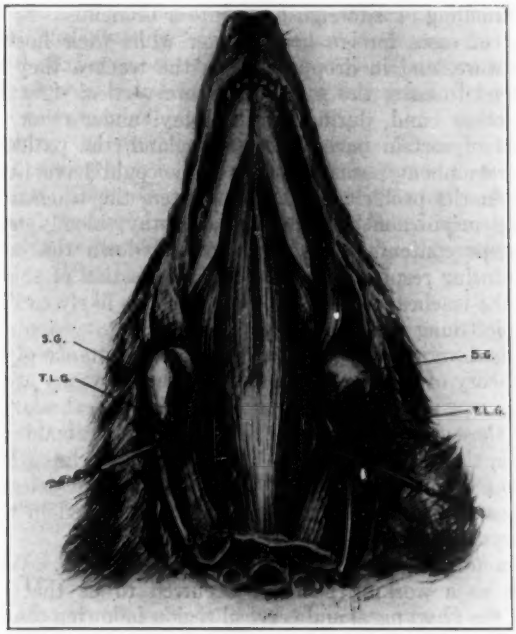


FIG. 1.—Author's drawing of a dissection of the neck, made after the tonsil region had been injected with a turpentine-ether solution of Berlin blue. The tonsil lymph node is shown, with its afferent lymph vessels. These vessels were traced back to the peritonsillar connective tissue. *TLG*, tonsil lymph node; *SG*, salivary gland.

his study of the same structure in man. The others were tonsillectomized. In one of them we removed one tonsil and left the other undisturbed, so that the tissues of the two sides subsequently could be compared. In the remainder both tonsils were removed: On one side two sutures were introduced and tied, while on the other an attempt was made to infect the raw surface by swabbing with bacteria. Before the sutures were passed they were soaked in a suspension of bacteria, these being actively hemolytic staphylococci and streptococci, the former having been isolated from the

blood of a case of staphylococcus septicemia and the latter from a case of acute pharyngitis.

Intratracheal ether anesthesia was used in each operation, and, in order to secure conditions well removed from the ideal, no antiseptic cleansing of the throat was done before operation and no sterilizing of hands, instruments or gauze was attempted. Two

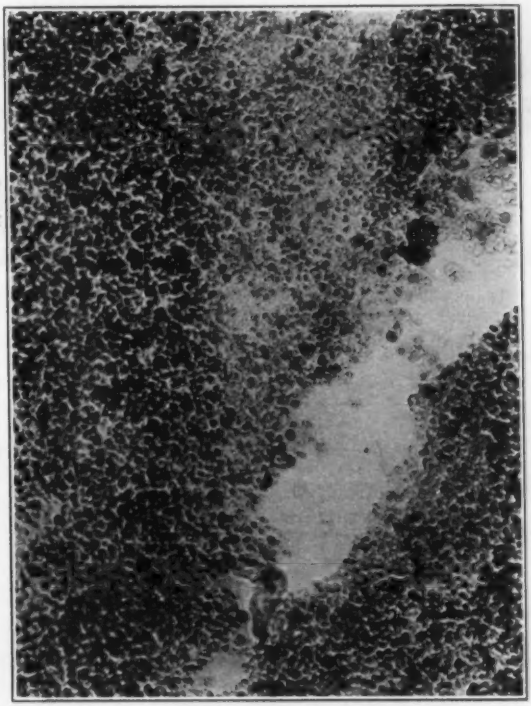


FIG. 2.—Tonsil lymph node, showing globules of pigment along cords. This specimen was taken from an animal which was killed one-half hour after the tonsil region had been injected with a turpentine-ether solution of Berlin blue. This was done to determine and identify the lymph node, which is next in series with the tonsil. It demonstrates how rapidly absorption from the tonsil into the lymph node takes place. The small globules of dye can be seen as innumerable black spots following the distribution of the lymphatic cords. No tissue stain has been used in this section.

of the animals were killed at the end of two days and the third after a lapse of four days. Various blocks of tissue were removed and studied histologically as well as for bacteria.

This part of the work was done in the Laboratory of Surgical Research of the University of Pennsylvania, and we are greatly indebted to Dr. J. Edwin Sweet for his helpful coöperation.

Results of Present Investigations. Study of our material, both gross and microscopical, has elicited the following facts:

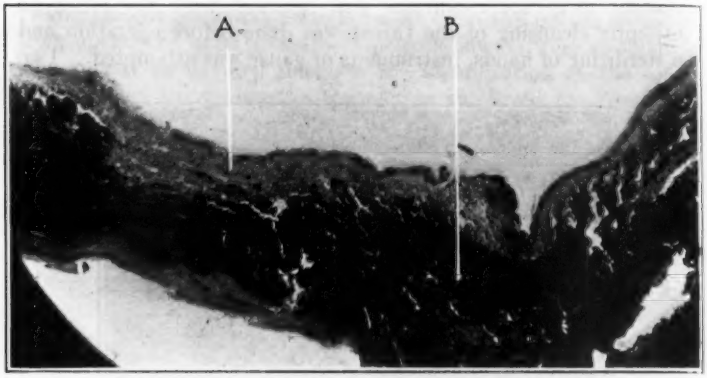


FIG. 3.—Tonsil pillar, showing submucous tissue distended with recent blood clot, two days after operation. This photograph illustrates one of the results of operative trauma on the tissue immediately adjacent to the tonsil. *A*, faucial mucosa and submucosa; *B*, muscular and fibrous tissue infiltrated with blood.

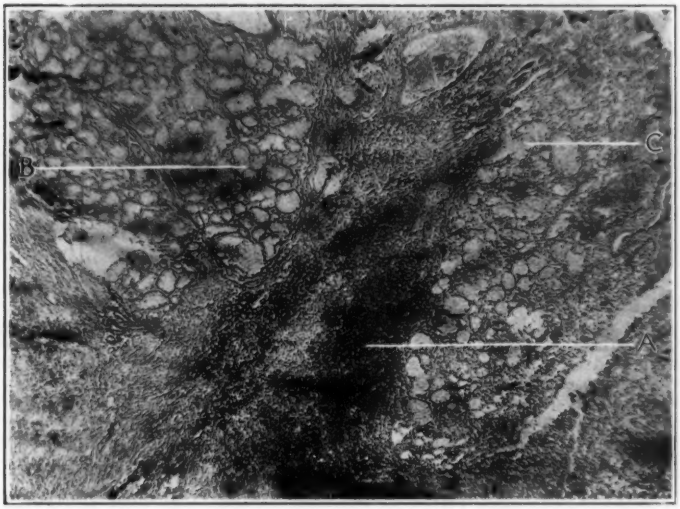


FIG. 4.—Salivary gland adjoining operation area. This specimen demonstrates hemorrhage into the gland as seen two days after operation. The hemorrhage shows as the dark structureless areas in the center and spreading out between the tubules. The pressure of the hemorrhage and the deprivation of blood supply have caused the gland cells to degenerate and the acini to lose identity; incidentally all parts lose contrast. *A*, hemorrhage; *B*, degenerating salivary gland, but some identity retained; *C*, more seriously destroyed salivary gland.

The Tonsil. The position of the tonsil in a narrow recess between and almost covered by the pillars, as depicted by Sisson,[15] was confirmed.

The Tonsil Lymph Node. The large lymph node lying under the occipitomandibularis muscle lateral to the pharyngeal wall and anterior to the sternomastoid was (Fig. 1) identified as the

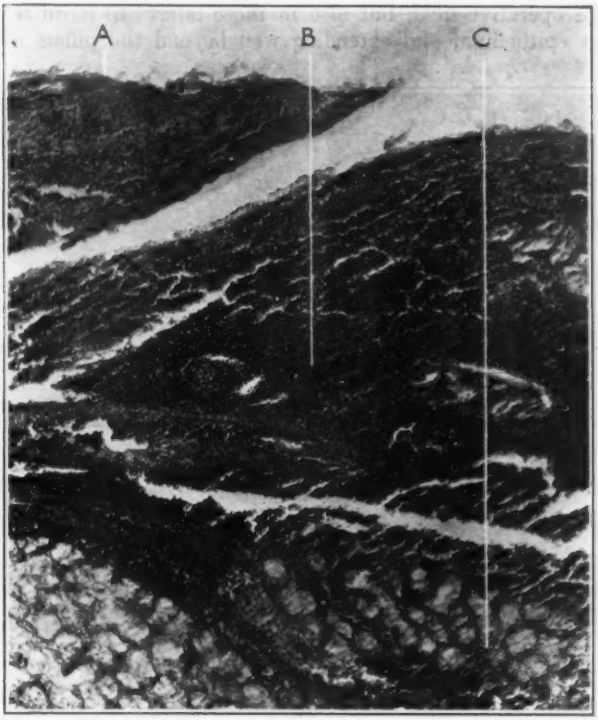


FIG. 5.—Operation field near salivary gland two days after operation. This picture shows hemorrhage and dense polynuclear and round-cell infiltration into the muscle tissue under the operation site and into the near-by salivary gland. *A*, raw operation field; *B*, muscle tissue with marked inflammatory cellular invasion; *C*, salivary gland with similar cellular invasion.

drainage node next in series to the tonsil. Turpentine-ether solution of Berlin blue injected into the tonsil was found to have drained rapidly (well under one-half hour) into this node. Lymph vessels were found, visible to the naked eye, connecting the lateral pharyngeal wall with this node. Dissection (Fig. 2) and microscopy of the tonsil revealed globules of the stain in the sinuses and along the cords of the tonsil, and also in the loose peritonsillar

connective tissue. In the lymph node (to be called hereinafter the "tonsil lymph node") it was found to some extent under the capsule, but mainly along the cords within the node.

Local Postoperative Effects of a Purely Traumatic Nature. The first effect of tonsillectomy, that of trauma, was found in our material principally as hemorrhage. There was a pouring out of blood (Fig. 3) not only into the tissues immediately subjacent to the operative field, but also in those lateral to it, under the intact epithelium, and extending well beyond the pillars of the

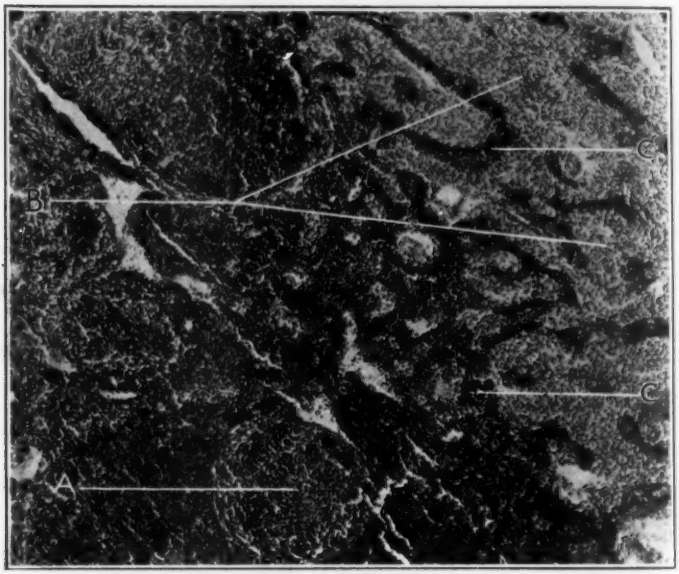
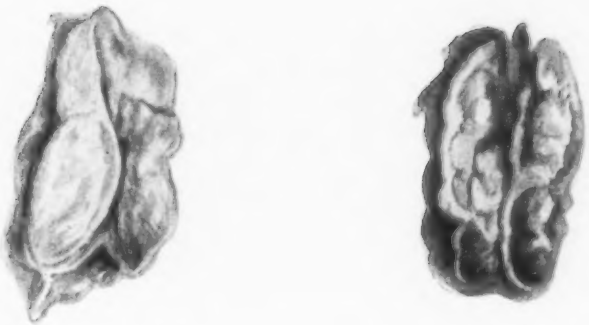


FIG. 7.—Section of the tonsil lymph node depicted in Fig. 6, *a*. The tonsil on this side of the body had not been removed. Specimen was removed two days after operation. While this node shows moderate activity in the follicles, all proportions are correct and the sinuses and cords are practically normal. *A*, follicle; *B*, sinuses; *C*, small normal cords.

tonsil (Fig. 4). In addition, hemorrhage was found in the adjacent salivary gland with resultant degeneration from pressure and impaired nutrition. Further reaction to the operative procedure was found in the form of round-cell and polynuclear infiltration, followed later by fibrino-cellular exudation, the latter varying with the infection (Fig. 5). This cellular infiltration reached the lateral and deep tissues, and among its sinister possibilities is destruction of these tissues, as happened to the salivary gland in these experiments.

Over the operation field a fibrino-cellular sheet was found, the



(a) (b)

FIG. 6

superficial layers of which are progressively cast off, just as false (Fig. 10) membrane loosens, until the healing area beneath it is completely exposed.

The Effect of Tonsillectomy upon the Tonsil Lymph Node without any Attempt Having been Made to Infect the Operation Wound. Two days after operation blood was present in the tonsil lymph node. The node was swollen and, when sectioned, was found to be so full of fluid (Fig. 6) that the cut surface was wet and greatly

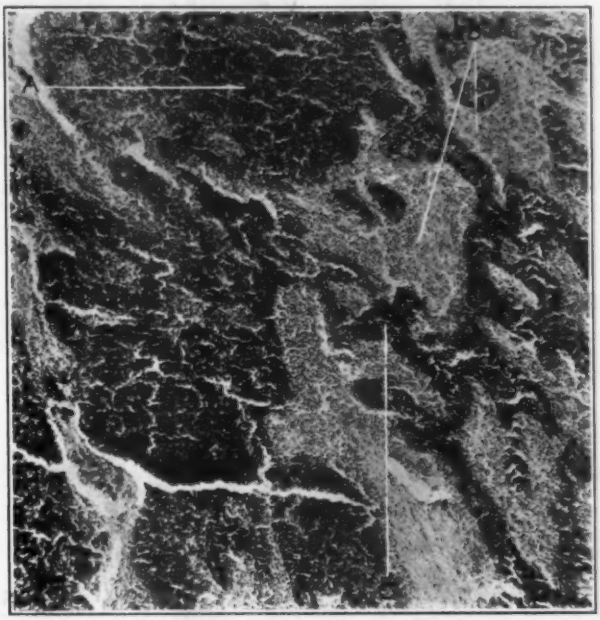


FIG. 8.—Section of the tonsil lymph node depicted in Fig. 6, *b*. The tonsil on this side of the body had been removed. Specimen removed two days after operation. The lymphoid tissue is very active and the markings are obscure, there being for instance no germ center in the two follicles in the picture. The sinuses are distended with blood, and the cords are wider than in Fig. 9. *A*, follicle showing activity; *B*, blood-filled lymph sinuses; *C*, cords.

congested. The node on the unoperated side was pale pink or yellowish and less wet.

Under microscopical study the node on the operated side was seen (Fig. 8) to be full of blood cells and their fragments, the sinuses especially being widely dilated. The lymphoid tissue itself was active in proliferation, but the follicular areas were not emphasized, there being instead a diffuse lymphocyte increase of all parts.

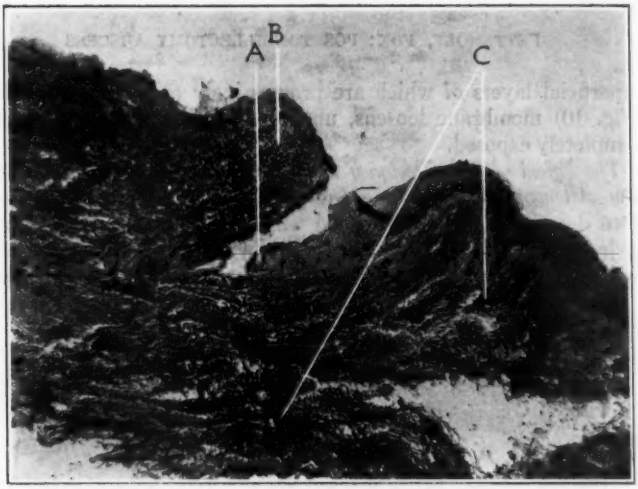


FIG. 9.—Edge of the operation site, showing postoperative exudate overlying the edge of the epithelium two days after operation. *A*, end of the epithelium at the edge of the operative field; *B*, edge of the postoperative exudate overlying, but here artificially separated from, the epithelium; *C*, blood under the epithelium at the site of the operated area.

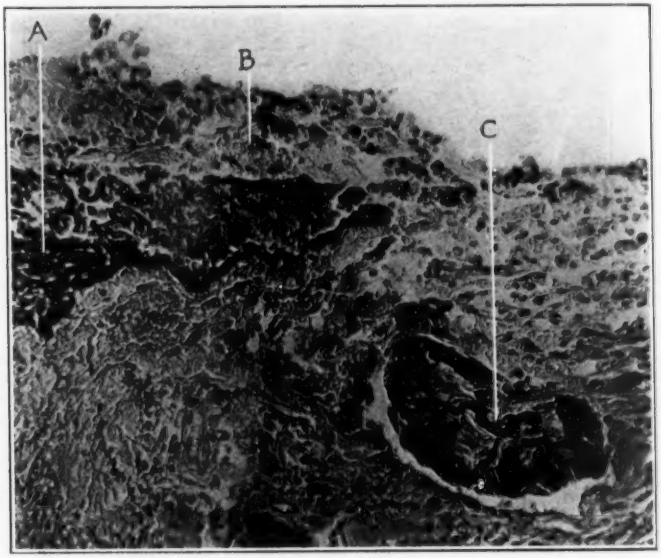


FIG. 10.—A portion of the operation field four days after operation, with the tissues stained for fibrin. The dark parts are fibrin. On the surface is an exudate consisting of two layers, a superficial light and a deep dark one. The former represents the actively degenerating part of the exudate, while the latter is the firm fibrinous exudate itself. The latter lies upon the healing operation base, and will itself later degenerate and be cast off. A well-formed thrombus lies in a vein just below operation area. *A*, fibrinous exudate; *B*, degenerated part of the exudate; *C*, thrombus.

On the unoperated side the node was found to be active in its (Fig. 7) follicular areas, but otherwise normal.

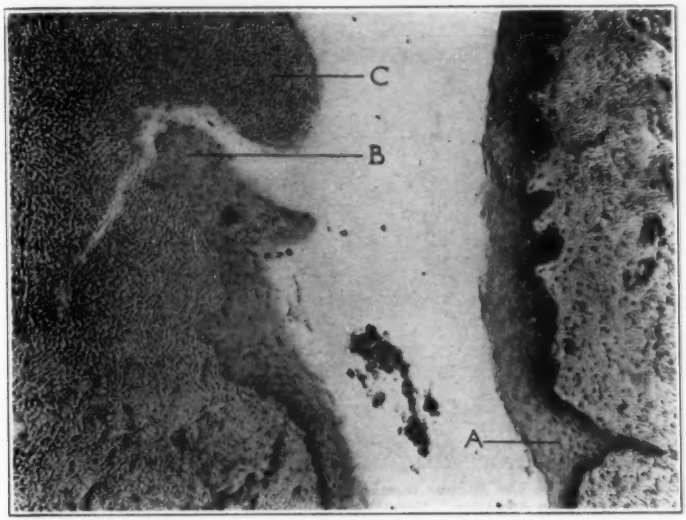


FIG. 11.—Tissue at the edge of the operation area, two days after operation. This figure shows the two lips of the wound, the one with undisturbed epithelium, the other at the cut edge where the epithelium is trying to spread but meets the exudate at the operation site. The epithelium is attempting to cover the raw surface but the exudate overlaps the proliferating surface cells. *A*, normal epithelium; *B*, inflamed epithelium at the edge of the wound; *C*, edge of the exudate overlying *B*.

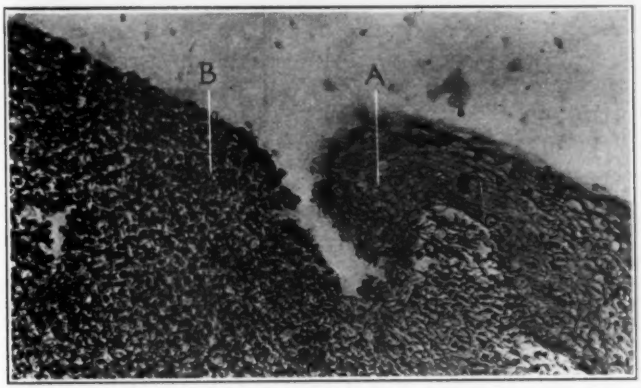


FIG. 12.—Edge of the tonsillectomy area, two days after operation. This figure shows the edge of the epithelium unable to make headway against the infected actively inflamed base of the operation site. *A*, edge of the epithelium; *B*, inflamed tissue showing the fibrino-cellular exudate developed at the operation site.

The Peritonsillar Results of Tonsillectomy which are not Purely Traumatic and which were Found when the Wound had been Artificially Infected. At the area of operation there was found,

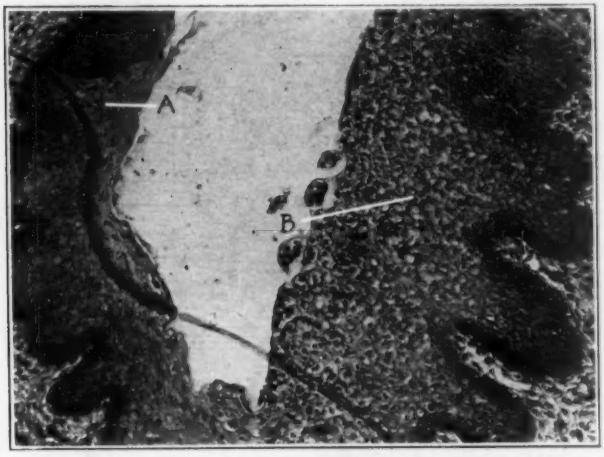


FIG. 13.—Fold in the mucous membrane adjoining the edge of the operation area, two days after operation. Normal epithelium at a distance from the wound. Actively inflamed epithelium adjoining the edge of the wound. *A*, normal epithelium distant from the wound; *B*, epithelium near the wound, showing active inflammation with many polymorphonuclears.

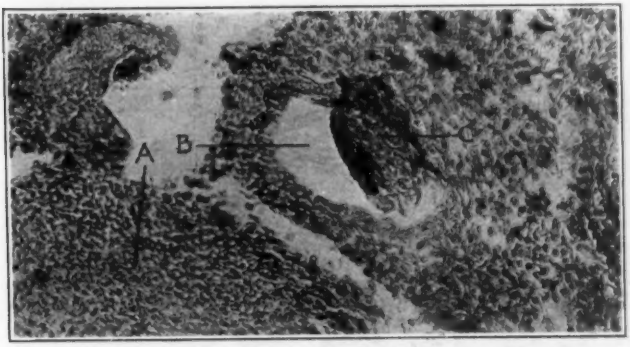


FIG. 14.—Base of operation site, two days after operation. This specimen shows dense infiltration, edema and a thrombosed vein. *A*, dense infiltration of round and polynuclear cells and much edema; *B*, thrombosed vein; *C*, thrombus artificially detached.

two days after operation, a well-developed fibrino-cellular exudate (Fig. 9). This not only covered the raw surface, but also extended laterally to overlie the edge of the adjacent epithelium. This exu-

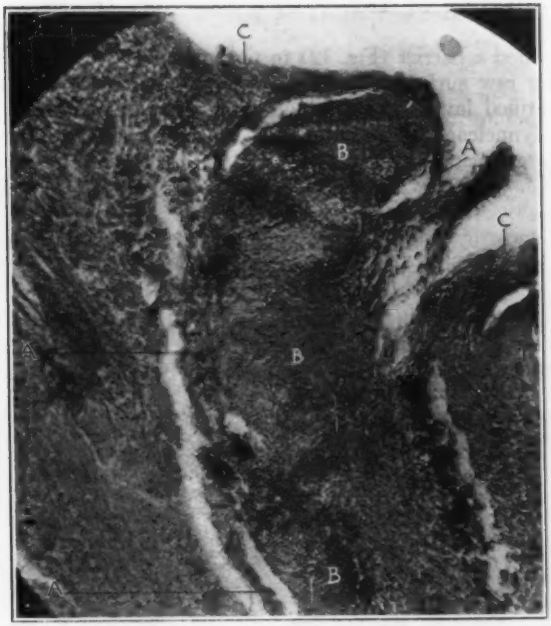


FIG. 15.—Thrombus in a vein just under the operation site, two days after operation. At several points the thrombus will be seen to be quite free from the lining of the vein, but at most of its periphery it will be seen to be closely attached. *A,A,A*, wall of vein; *B,B,B*, thrombus; *C,C*, raw operation field.

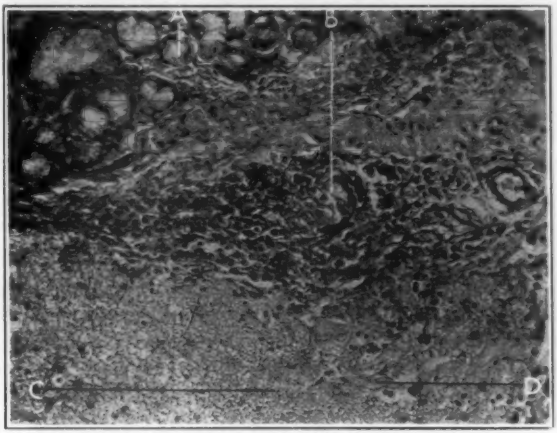


FIG. 16.—Deep tissue beneath the operation site, two days after operation. This specimen shows vacuolated salivary gland cells, and separation with destruction of a small piece of salivary gland by cellular infiltration. It also shows edema and degeneration of a large area of muscle, small strands of which are recognizable. *A*, salivary gland with vacuolated cells; *B*, isolated island of salivary gland surrounded by cells and edema; *C*, degenerated muscle, strand remnants of which are seen at *D*.

date formed a barrier (Fig. 12) to the extending of the epithelium over the raw surface. In addition, when infection was present the stratified layers of epithelium were seen to be thickly beset with polynuclears (Fig. 13) and in a state of active inflammation, this decreasing as the distance from the operation site increased (Fig. 10). The exudate lay upon a tissue base characterized by a reactive cellular inflammation.

A noteworthy finding in this inflamed part was the congestion of all varieties of vessels and the frequency of thrombi, both near the surface and deep in the tissues (Figs. 14 and 15). These thrombi were attached to the vessel wall and were well developed by the end of the second day. No signs of softening were observed in any of them.

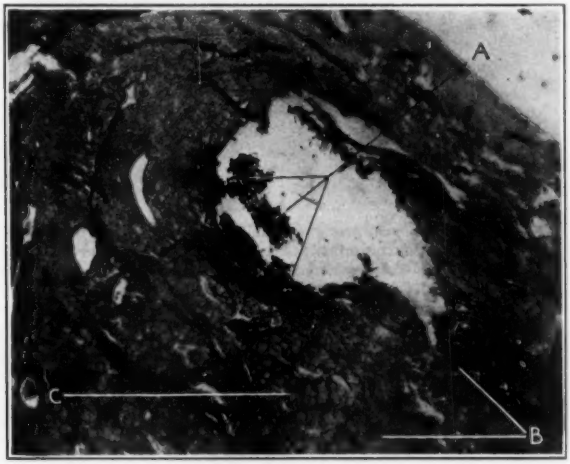


FIG. 17.—Silk stitch and adjacent area, under low magnification, four days after operation. Most of the stitch fibers have fallen out of the section. This picture shows a healthy reactive area around the stitch, with some degeneration of muscle and salivary gland tissue. *A*, fibers of the suture; *B*, degenerated muscle; *C*, degenerated salivary gland.

Study of the deeper tissues of the tonsillectomy area showed the inflammation to be similar to that near the surface, including a feature already noted, viz., the involvement of the salivary gland (Fig. 16). In addition the fibrino-cellular exudate was seen to extend well into the muscle tissue (Fig. 15), and many small thrombotic veins were here encountered.

The Local Effect of Sutures. The suture tracks were found to be surrounded by a mild fibrino-cellular reaction, highly cellular at the end of two days (Fig. 17), and showed signs of healing at the end of four days. The tissue caught by the stitch was com-

pressed and degenerated, particularly the muscle and salivary gland tissue (Fig. 18). Small patulous capillaries were found in the healing area, but the large veins usually were thrombotic.

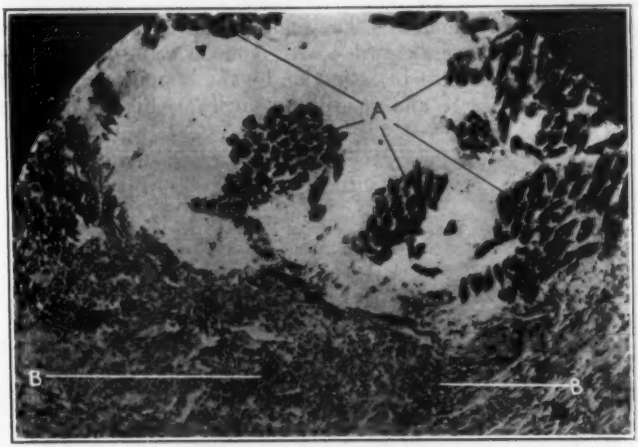


FIG. 18.—This picture shows the stitch and its adjacent tissue, under high magnification, four days after operation. *A*, strands of the stitch; *B,B*, healthy reaction to the stitch, some round-cell infiltration in small groups, but no abscesses.

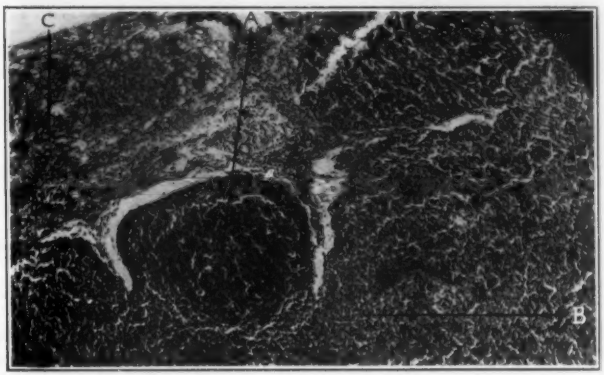


FIG. 19.—Tonsil lymph node, two days after operation, on the side of which infected stitches were used to close the wound of tonsillectomy. This node shows a very active hyperplasia, as indicated by the size and solidity of the follicles, a degree of compactness of the intervening lymphoid tissue great enough to obliterate the sinuses. In addition, there are congestion of the capsular vessels and distention of the lymph ducts. In certain of the capsular lymph channels some swelling and degeneration of the lining were found. Bacteria were found in these lymph ducts. *A*, hyperplastic follicle; *B*, solid cordal area without visible sinuses; *C*, swollen, congested and edematous capsule.

The Tonsil Lymph Node after Operation Plus Artificial Infection of the Operation Wound. The tonsil nodes after an infected operation were very large, soft, wet and irregularly congested, especially at the capsule (Fig. 19). Under magnification a very marked hyperplasia was found, differing greatly from conditions depicted in Figs. 9 and 10. The follicles showed large germ centers and the cords were crowded with mononuclears. The sinuses were compressed almost to extinction by the lymphoid increase or were filled with large and small mononuclears (Fig. 21), as well

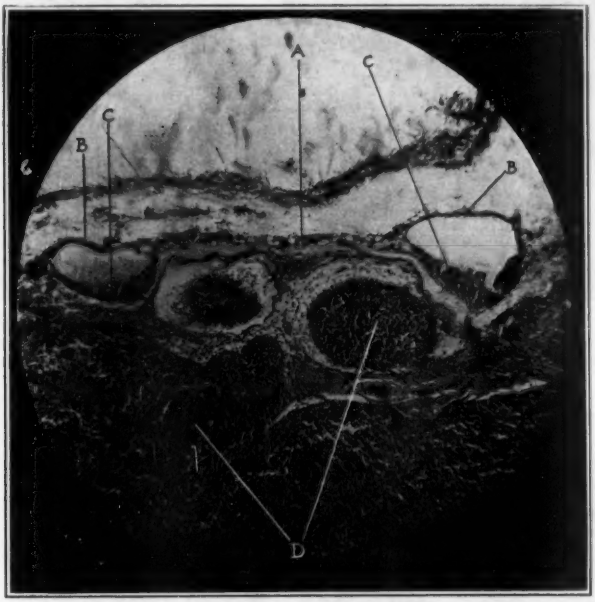


FIG. 20.—The same lymph node as that from which section shown in Figs. 19 and 21 were taken. It shows dilated lymph vessels with postmortem clots. A small group of bacteria was found in one of these clots near the lining of the vessel. Solid hyperplastic follicles of the node lie under the capsule. *A*, capsule of the lymph node; *B,B*, lymph vessels; *C,C*, coagula; *D*, follicle.

as with endothelioid and polynuclear cells. This last change was best seen near the hylum of the node. In addition, the increased size of the lymph vessels was quite notable. They were greatly dilated and were almost completely filled with a hyaline postmortem lymph clot (Fig. 20), this being especially notable in the capsule. Bacteria were found in or near the lining of these vessels.

It should be stated in this connection that a superior mediastinal lymph node of one animal showed a similar hyperplasia. There were present also dilated lymph vessels, small hemorrhages

and very marked degeneration of the follicular centers. Bacteria were not surely found.

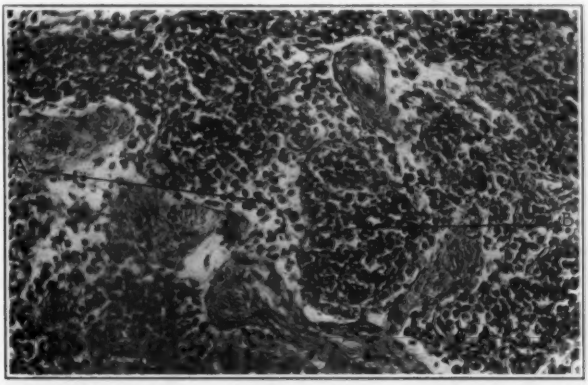


FIG. 21.—The same lymph node as that from which sections shown in Figs. 19 and 21 were taken. Central area of the node under high magnification. This specimen shows the cellular richness of the central sinuses. Numerous lymphoid cells of all varieties, polymorphonuclears and large mononuclears of endothelioid proportions were found in the well-crowded spaces. The cords are very thin at this point. *A*, a crowded sinus; *B*, the end of a small cord.

Bacterial Distribution. Bacteria in those cases which were artificially infected were found with ease in the stitches and in the

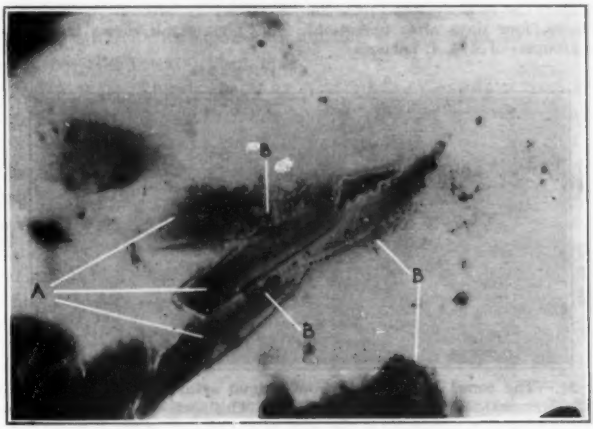


FIG. 22.—A strand of silk with bacteria in it, four days after operation. (Oil immersion exposure.) *A*, fibers of silk; *B,B,B*, bacteria.

area immediately surrounding them (Fig. 22). As distance from the stitch region increased the microörganisms became fewer and

fewer. They were traced along one tissue split into a muscle area (Fig. 23), and also were found in a salivary gland.

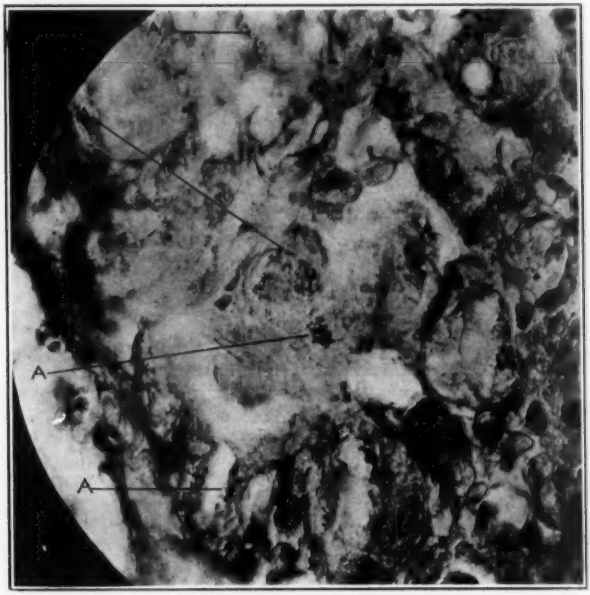


FIG. 23.—The salivary gland from animal artificially infected by stitches soaked in cultures, four days after operation. This photograph shows bacteria singly and in groups. *A,A,A,A*, bacteria.

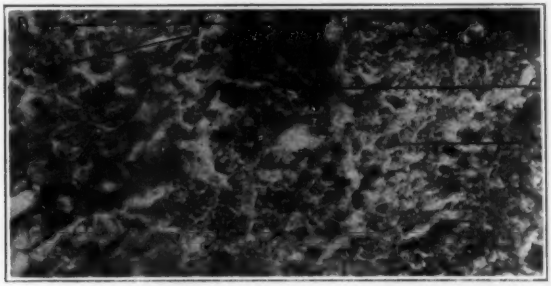


FIG. 24.—The tonsil lymph node from animal artificially infected by stitches soaked in cultures, four days after operation. This section shows bacteria on the edge of a cord and in a necrosis at the edge of a cord. *A*, cord; *B*, necrosing area; *C,C,C*, bacteria.

In the tonsil lymph node bacteria were present in pairs and in small clumps. They were found in the dilated capsular lymph

vessels (Fig. 24), in the subcapsular (the so-called "marginal") sinus and in the interior sinuses near the edges of the cords.

They were not found with unequivocal certainty in the thrombosed vessels.

Summary of Results. Injected material found its way from the tonsil to the first drainage lymph node in half an hour or less.

Tonsillectomy traumatism was manifested not only at the immediate operation site, but also in the collateral tissue in the form of hemorrhage and cellular infiltration.

The surface of the wound was covered with a fibrinous exudate, the outer layers of which were progressively cast off.

The tissue reaction at the site of operation was degenerative and fibrino-cellular, the former appearing at once, the latter being in part the result of traumatism and in part the natural successor to degeneration, and therefore the early stage of repair.

Exudate of a fibrino-cellular character was found deep in the tissues, with resultant degeneration of muscle and salivary gland tissue.

Many venous thromboses were found both near the surface and deeper.

The tonsil lymph node reacted to moderately clean operative procedures by caring for the extravasated blood and by mild hyperplasia.

To a purposely infected operation the reaction of the lymphatic tissue was very marked, so much so that the lymph current probably was obstructed.

Each attempt at artificial infection succeeded and important structures, such as muscles and glands, were found to have been invaded by the microörganisms.

Bacteria were found easily in the surface exudate and in the vicinity of infected stitches. They also were found in the salivary glands and in the tonsil lymph nodes.

When bacteria-soaked stitches were introduced the infected or at least inflamed, area was thereby made deeper, while important tissues were compressed and distorted.

While not certainly demonstrated in the thrombi near the operation wound, we believe that bacteria sure must be there. The fibrin was so dense (having taken the same stain as did the bacteria) that their definite identity was obscured.

* * * * * * * * * *

We have shown graphically what happens around a tonsillectomy wound. In a word, there are present hemorrhages, thrombi, necroses and bacteria. Hemorrhage causes rifts in the tissues, opens pathways for infection and destroys tissue. Trauma and disturbed blood supply result in necrosis. Injured bloodvessels are closed by coagula whieh may become infected and loosened.

Bacteria are carried into the tissues by physical force or are permitted to penetrate by the opening up of tissue clefts, especially when there has been some devitalization. These are present in an area which never can be put at rest, which constantly is open to reinfection and which is subjected to a great deal of constrictor muscle action.

What might be the consequences? Should a sterile thrombus be dislodged into the blood the result would be a small sterile pulmonary infarct which, however, later may become infected and give rise to pneumonia or an abscess. Should a septic thrombus be dislodged a lung abscess would be the probable result. Should a thrombus, either sterile or septic, reach a previously diseased area of the lung, such as a tuberculous focus, the lesion might be activated.

As yet there has been no postoperative study of tonsil cases in which the lungs have been carefully watched for small lesions. Lung infarctions after tonsil operations naturally would be small on account of the size of the peritonsillar veins, and it is perfectly possible that many a lung infarct caused by a non-septic embolus has escaped notice. *We would like to emphasize the following point:* One of the early signs of pulmonary infarction is the spitting of bright red blood, and it is quite possible that at times some of the blood-spitting in the early days following tonsillectomy is due to an overlooked infarction and not to oozing from the operation field. In our clinical work it might be well to keep this in mind and let this sign be a signal to examine the larynx and trachea as well as the tonsil fossæ, and also to have the chest examined and roentgen-rayed.

Conclusions. 1. The peritonsillar region as depicted in our specimens constitutes a postoperative field studded with thrombi, which may be either sterile or septic.

2. We believe that as trauma, sepsis and muscular action are the principal factors in the formation and dislodgment of thrombi, the actively muscular pharynx is a particularly favorable region for the dislodgment of such thrombi into the superior caval circulation.

3. We believe that many cases of pulmonary embolism escape notice on account of their small size, their sterile character and their prompt resolution.

4. It goes without saying that the performance of tonsil operations should be attended with every possible surgical device for promoting asepsis. We suggest, in the furtherance of this principle, that the routine use of needle-carried sutures for tying bleeding vessels be abolished and that surface ties be used instead.[16] The former are never surgically clean and we believe that their use carries with it possibilities of infection of at least the tissues adjacent to them.

5. While realizing that posttonsillectomy lung complications may at times be of inspiratory origin, we believe that such origin is not as common as has been thought.

6. While the infected condition of the lymphatic tissue found in our study must cause consideration to be given to a lymphatic origin for lung infections, we consider such origin to be rare.

7. Finally, it is possible that, in view of such studies as the present one, ideas in regard to the capsule of the tonsil may undergo a change. Instead of aiming to remove it, we may decide that it forms too good a bulwark to the peritonsillar tissues to allow of its being taken away. And we believe it to be entirely possible that some day the operation, called by Makuen[17] "intracapsular tonsillectomy," will be so demanded by the highest ideals of safety that in a perfected form it will be the operation performed by all of us.

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ODD CARBON FATS IN THE TREATMENT OF DIABETIC KETOSIS.

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It was shown by Knoop,[1] in 1905, that fatty acids in combination with aromatic radicals when given to animals are oxidized in a definite manner in the animal organism. It is known that if benzoic acid is administered by mouth it is excreted in the urine in conjunction with amino-acetic acid as hippuric acid, thus:

$$C_6H_5COOH + CH_2NH_2COOH = C_6H_5CONHCH_2COOH + H_2O$$

Phenylacetic acid is eliminated as phenaceturic acid:

$$C_6H_5CH_2COOH + CH_2NH_2COOH = C_6H_5CH_2CONHCH_2COOH + H_2O$$

If a higher acid than acetic acid is administered the resultant product eliminated is either the hippuric acid or the phenaceturic acid, depending upon the fact whether the side chain was of an odd or even number of carbon atoms. Knoop, therefore, concluded that in the oxidation of fats the β-carbon atom was oxidized and that two carbon atoms dropped from the chain together. This view was supported by Dakin's[2] discovery that when phenyl propionic acid was given in large amount phenyl β-oxypropionic acid was detected in the urine.

In this excellent summary on "Physiological Oxidations," Dakin[3] reviews the modern status of the theory of oxidation of fatty acids. I quote several of his paragraphs:

"In spite of a good many vigorous onslaughts, the theory of β-oxidation applied to fatty acids as put forward originally by Knoop has held its own. It will be recalled that one of the main supports of Knoop's views was furnished by Embden's observation that the normal fatty acids containing an even number of carbon atoms varying from 4 to 12 all gave rise to aceto-acetic acid when their salts were perfused through a surviving liver. The normal fatty acids containing an uneven number of carbon atoms failed to cause any increase in aceto-acetic acid production. An interesting clue to the probable fate of some of these normal fatty acids has been furnished by Ringer, who finds that propionic acid is practically quantitatively converted into glucose in the phloridzinized dog and that normal valeric and heptylic acids give an amount

[1] Hofmeister's Beiträge, 1905, **6**, 150.
[2] Jour. Biol. Chem., 1909, **6**, 203.
[3] Physiol. Rev., 1921, **1**, 406.

of glucose under similar conditions comparable to the amount of propionic acid they might yield through β-oxidation:

$$CH_3.CH_2.CH_2.CH_2.CH_2.CH_2.COOH \rightarrow CH_3.CH_2.CH_2.CH_2.COOH \rightarrow CH_3.CH_2.COOH$$

"Blum and Woringer have recently shown that when propionic acid is given to normal dogs and rabbits, lactic and pyruvic acids are excreted, and these undoubtedly represent intermediary products of the oxidation of propionic acid, although it is not clear as to which of these two acids is first formed or whether perchance they are formed from acrylic acid, which Schwenken has shown to be almost quantitatively converted into glucose in the phloridzinized dog. The conversion of propionic acid into lactic acid explains the conversion of the former acid into glucose in the phloridzinized animal, for, as is well known, the conversion of lactic acid into glucose under these conditions is virtually quantitative. The formation of lactic and pyruvic acids from propionic acid must be regarded as a case of α-oxidation, though possibly indirect, but since normal β-oxidation with formation of ketonic acid is no longer possible with a three-carbon acid it need not be regarded as violating the β-oxidation rule applicable to acids containing four or more carbon atoms. It appears, therefore, that in the metabolism of normal fatty acids containing four or more carbon atoms aceto-acetic acid is a common metabolite of all those with an even number of carbon atoms, while lactic acid is common to those with an uneven number."

In the catabolism of fats (under normal conditions, that is, in the presence of proper carbohydrate oxidation) there is a rapid breakdown of the fatty acid radical to the four-carbon acid, *i. e.*, butyric acid:

$$\begin{array}{l} CH_2-OOC-CH_2-CH_2-CH_2-R \\ | \\ CH-OOC-CH_2-CH_2-CH_2-R \\ | \\ CH_2-OOC-CH_2-CH_2-CH_2-R \end{array} \longrightarrow \begin{array}{l} COOH \\ \vdots \\ CH_2 \\ \vdots \\ CH_2 \\ \vdots \\ CH_3 \end{array}$$

The butyric acid is then rapidly catabolized to carbon dioxide and water.

This process is, however, markedly disturbed in states of deficient carbohydrate oxidation. In the latter circumstance the fats are primarily broken down to butyric acid, as in the normal condition, but in the absence of the heat of carbohydrate consumption the further decomposition of the butyric acid proceeds very slowly. The butyric acid under these conditions is decomposed first to β-oxybutyric acid and then to aceto-acetic (or diacetic) acid. The further decomposition to acetone takes place very largely in the urine itself.

$$\underset{\text{I.}}{COOH.CH_2.CH_2.CH_3} \rightarrow \underset{\text{II.}}{COOH.CH_2.CHOH.CH_3} \rightarrow \underset{\text{III.}}{COOH.CH_2.CO.CH_3} \rightarrow \underset{\text{IV.}}{CH_3.CO.CH_3}$$

I	Butyric acid.
II	Beta-oxybutyric acid.
III	Aceto-acetic acid.
IV	Acetone.

Rosenfeld has said that fats burn only in the fires of carbohydrates, but this is not quite right, inasmuch as only the breakdown of the lowest products of fat decomposition, that is to say, the acetone substances, depends upon the catabolism of the carbohydrates.

How does the fat decompose to butyric acid? Of the two components of fat, only the fatty acids yield the ketone substances. The glycerin portion of the fat molecule is antiketogenic in nature. "By investigations performed either with living beings in a state of acidosis or with the transfused dog's liver, it has been established that fatty acids are broken down by a repeated splitting off of two carbon atoms. The first step is the formation of the β-oxy acid, which is then transformed to the β-keto acid:

$$COOH.CH_2.CH_2.CH_2::R \rightarrow \underset{::::\beta\text{-keto acid}}{COOH.CH_2.CHOH::::\beta\text{-oxy acid}} \rightarrow COOH.CH_2.CO$$

The transformation requires a two-fold oxidation at the β-carbon atom. Contrary to what happens in the lungs with aceto-acetic acid, a splitting off of the carboxyl group and the formation of true ketone generally does not take place in the metabolism; instead we find a simultaneous splitting off of the carboxyl group and of the α-carbon atoms, thus yielding a new fatty acid lower by two carbon atoms." (Magnus-Levy.)

Embden has found that only fatty acids of an even number of carbon atoms will yield aceto-acetic acid in the transfused dog's liver. In this way from stearic acid (C_{18}), palmitic acid (C_{16}) is formed; from this an acid with 14, 12, 10 or 8 carbon atoms is derived. Then caproic acid (C_6) and, finally, butyric and oxybutyric acids are formed. The relative figures are as follows:

	Molecular weight.	Relation of molecular weight.	Per cent yield of oxybutyric acid from 100 gm.
C_{18}	284	100.0	36.5
C_{16}	256	90.0	40.0
C_{14}	228	80.0	46.0
C_{12}	200	70.5	52.0
C_{10}	172	61.0	60.0
C_8	144	51.0	72.0
C_6	116	41.0	90.0
C_4	88	31.0	118.0
Oxybutyric acid, 104		36.5	

Several years ago[4] I endeavored to see the effect of the feeding of a fat containing an odd carbon fatty acid.

We have succeeded in preparing an odd carbon fatty acid fat that is edible, is absorbed to the extent of about 90 per cent, is catabolized in the body and does not yield the ketone substances derived from butyric acid.

The methods of preparation is as follows:

Stearic acid has its acid group substituted by an organic radical and upon oxidation with a strong oxidizing mixture the C_{17} acid ($C_{16}H_{33}COOH$, margaric acid) is produced. This is easily purified and then united with glycerol to form a neutral fat.

This fat, when well prepared, is of a white creamy color, odorless and tasteless, melting at 38° C. and neutral in reaction. When cold and granulated it is quite palatable. It does not cause any sense of nausea, and it seems to satisfy the hungry craving for fat that diabetics have. A number of patients were fed the fat, but it will be sufficient to describe 3 cases as the results are typical.

EXPERIMENT I.—It was thought advisable to induce ketosis in a normal individual and then see the effect of our fat on this ketosis. Accordingly, we advertised in the newspapers for a normal man willing to submit himself to a fasting experiment. From the many applicants, we chose A. A., aged twenty-three years, white, born in Sweden, who was by trade a cement worker and ofttimes a prizefighter. He was 5 feet 10 inches tall and weighed 144 pounds. He was in perfect physical condition. He undertook this task for the money that he was to receive.

He was placed in a separate room, with a male nurse in attendance. No food was given him whatsoever. Water was permitted as much as he wanted. He was fasted for seventy-four hours. His urine at the end of that time had marked quantities of diacetic acid and acetone. He was now given 100 gm. of our fat mixed with 100 gm. seven-times boiled string beans. Next day the urine was clear of acetone and diacetic acid. He was now given 100 gm. butter in 100 gm. seven-times boiled string beans. The urine next day showed again the ketone substances. During this day he received 200 gm. of the odd carbon fat in string beans and again his ketosis cleared up.

He was then discharged. His feces was analyzed (Dr. H. O. N.) and was found to contain 5 per cent of the ingested fat. The rest had been absorbed.

The subject did not complain of nausea or of any distaste for the fat. On the contrary, the butter was more distasteful to him than was our fat.

[4] About ten years ago Ringer suggested the use of such a fat. He was, however, unable to prepare one. Mosenthal also wrote of the desirability of such a fat.

The accompanying table shows the results obtained.

DATA ON FASTING EXPERIMENT.

Date.	Urine.					Blood.				Alv. air, Frederician.	Remarks.
	Vol., cc.	Sp. gr.	Acetone.	Diac. acid.	NH_3, gm.	CO_2, per cent.	Urea, N.	Creat., mg.	Glucose, per cent.		
June 12	....	1.021	○	○	....	50	20.4	1.25	0.1	5.4	Began fast 1 P.M.
June 13	640	1.030	○	○	0.75	..	....	....	....	5.2	Fasting.
June 14	1460	1.016	○	○	1.38	..	....	....	....	4.8	Fasting.
June 15	1350	1.018	++ ++	++	3.25	37	....	....	0.08	4.0	3 P.M. received 100 grams *Intarvin* and 100 grams 7x washed string beans.
June 16	1480	1.014	○	○	1.45	45	....	....	0.08	4.6	1 P.M. received 100 grams butter and 100 grams 7x washed string beans.
June 17	1220	1.016	++ +	+	3.80	37	....	....	0.08	4.1	Received during day 200 grams *Intarvin* and 100 grams 7x washed string beans.
June 18	1430	1.018	○	○	2.75	48	15.7	2.25	0.06	4.8	

EXPERIMENT II.—A diabetic woman (A. S.), aged forty-seven years, was admitted to the gynecological service with the diagnosis of tumor of the adnexa. She had been under my care previously for a year. She had lost much weight and was in a condition of acidosis and hyperglycemia and glycosuria when admitted to the hospital. I urged the surgeon to wait with the operation until we could render her non-ketotic, but this was found to be impossible at the end of ten days, although she was kept on a diet fat-free as possible. She was catabolizing her body fat and her urine was heavy with diacetic acid and acetone.

A. S.

Date.	Food, gm.				Urine.		Blood.		
	P.	CH.	F.	Odd fat.	Glucose.	Diac. acid.	Acetone.	CO_2, per cent.	Glucose.
Nov. 29, 1921	..	..	..	..	....	....	....	44	0.25
Nov. 30, 1921	39	16	22	0	40.9	+++	+++		
Dec. 1, 1921	31	19	17	0	32.6	+++	+++	42	0.23
Dec. 3, 1921	42	15	8	0	27.9	++++	+++		
Dec. 6, 1921	60	15	4	0	31.4	++++	+++	44	0.22
Dec. 7, 1921	45	15	4	90	....	○	+++		
Dec. 8, 1921	45	15	4	90	Trace	○	○	56	0.17

To the same fat-free diet we added a daily ration of our fat of 3 ounces. The patient, it seemed, aridly absorbed this fat and in forty-eight hours the urine was free from diacetic acid. This case was rather puzzling to us, for not only did her ketosis cease, but her glycosuria was markedly diminished.

The cause of ketosis, the most common form of which is the acidosis of diabetes, is a disturbance in the catabolism of the fats induced by either starvation, infantile malnutrition or anesthesia induced by lipin solvent anesthetics besides diabetes. We have studied the ketosis of diabetes and starvation and it is expected in the near future that tests on the other types of ketosis will be carried out.

EXPERIMENT III.—A. S., male, aged forty-four years, married, with two children. For the past five years the patient has had diabetes. One year and a half ago he weighed 185 pounds. He was then removed to a sanitarium and put on the undernutrition treatment so that he lost 110 pounds. For the past several months he has been in bed suffering from general furunculosis, cachexia and pulmonary tuberculosis. He was unable to get out of bed, attend to himself and so on.

In order to keep him sugar-free and ketone-free he was kept on a diet of about 500 calories daily, with a fat intake of 34 gm. and a carbohydrate intake of 8 gm.

The patient was brought to the hospital in this very serious condition. The addition of several grams of fat to the diet in the form of butter or egg-yolk immediately brought about an acetone reaction in the urine.

We, therefore, placed the patient on a diet of protein, 38 gm., carbohydrate, 8 gm., and fat, 34 gm. In addition to this we gave him daily 150 gm. of the "odd carbon" fat, thus increasing his caloric intake from about 500 calories daily to about 1700 calories.

He relished the fat. His hunger was allayed. During a period of ten weeks he gained 10 pounds in weight. His urine remained free from sugar (except for faint traces on three days during a period of nearly four months). His fat catabolism was normal; no acetone nor diacetic acid appeared in his urine. His carbon-dioxide combining power of the blood plasma was normal.

His tuberculosis, however, was not improved. It became necessary to send him to a hospital for the care of tuberculosis because of his expectoration and cough. Several weeks after his transfer he died from a pulmonary hemorrhage.

The data that are of interest in this case are presented in the accompanying table. It was observed that the addition of any normal fat, either inadvertently or purposely, resulted in the appearance of the ketone substance in the urine.

A. S.

Date.	Food.				Urine.		Blood.	
	P.	C.	F.	Odd fat.	Glucose, per cent.	Ketones.	Glucose.	CO_2.
Feb. 20 . .	40	20	42	0	Traces	++	0.224	44
Feb. 22 . .	40	35	40	. . .	1.4	++	0.227	46
Feb. 24 . .	37	13	31	0	0	○	0.185	48
Mar. 2 . .	40	20	42	0	Traces	++	0.195	42
Mar. 6 . .	37	13	31	0	0	○	0.175	48
Mar. 10 . .	42	15	37	0	0	○	0.162	48
Mar. 14 . .	42	15	37	100	0	○	0.151	54
Mar. 20 . .	42	15	37	100	0	○	0.148	54
May 24 . .	42	15	37	150	0	○	0.113	58
June 8 . .	44	17	37	150	0	○	0.134	58

EXPERIMENT IV.—R. G., aged twenty-five years, was suffering from pituitary glycosuria with marked emaciation and loss of weight. She weighed 75 pounds and showed distinct evidence of ketone substances in the urine. Upon feeding of the odd carbon fat the acetone cleared up and during a period of several months she gained 10 pounds in weight. It is worthy of note in this case that the administration of insulin had absolutely no effect on the presence of the glycosuria or in the control of the loss of weight.

The accompanying table shows some of the figures obtained.

R. G.

Date.	Food.				Urine.		Blood.	
	P.	C.	F.	Odd fat.	Glucose.	Ketones.	CO_2.	Glucose.
Feb. 9, 1922	62	36	90	0	3.2	++++	48	0.23
Feb. 11, 1922	60	20	68	0	1.7	+++	..	0.24
Feb. 12, 1922	57	16	20	90	0.6	++	..	0.21
Feb. 13, 1922	60	12	18	90	○	○	58	0.16
Feb. 15, 1922	62	17	40	0	+	+++		
Mar. 4, 1922	60	18	15	100	+	○	56	0.17

The fat is administered by mouth in the following ways: (1) Granulation of the fat and direct consumption with the aid of salt, pepper or vegetables; (2) baking with the fat: it was used in the preparation of Lister's bread, etc.; (3) frying with the fat after "rendering" it with onions; (4) in the form of an ice-cold emulsion in buttermilk, etc.; (5) in the form of a flavored drink; (6) with hot drinks, such as coffee, broth, etc.

Summary. 1. Ketosis is due to the pathobolic breakdown of fats in the absence of carbohydrate oxidation.

2. Natural fats are all glycerides of fatty acids containing an even number of carbon atoms, which during abnormal breakdown yield butyric acid and the ketone substances of diabetic ketosis.

3. An odd carbon fatty acid fat has been synthesized which is palatable, is absorbed to about 90 per cent and is catabolized in the body of diabetic patients without the production of ketones.

4. The diabetic patient's diet can be much increased by this fat. It allays hunger and stops the loss of weight.

5. It may be fed *ad libitum*.

FURTHER OBSERVATIONS ON ARTHRITIS AND RHEUMATOID CONDITIONS.

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About three years ago the writer published an article,[1] based somewhat upon researches conducted on a large scale in the army,[2] in which the attempt was made to correlate into a whole, some of the demonstrated and suggested facts regarding the problem of arthritis, with the aim of visualizing at least part of the pathology of arthritic and rheumatoid conditions. Since then, further data and viewpoints have been arrived at sufficient to justify a recapitulation: This is attempted in the present contribution.

In the study of large subjects like arthritis, diabetes, arteriosclerosis and metabolic disturbances in general, it is obvious that the solution is rarely to be expected from a single experimental *coup de grâce*. The situation differs from that presenting in certain purely bacteriological or parasitic diseases where the discovery of a causative organism may largely clear up the field. While it is known, for example, that many cases of arthritis are precipitated by streptococci and other organisms, acting through so-called focal infections, other cases are apparently precipitated by different factors and in any event the mechanism concerned in the production of the symptoms and lesions has remained entirely obscure.

The true conception of diseases such as those mentioned must come from the piecing together of a host of data in many fields, chiefly physiological in nature. It is probable that for some time at least, anything like a full understanding of these conditions, based solely upon exact data, will be beyond our power and it becomes therefore appropriate and necessary to make such reviews of the field from time to time as new and changing data permit.

In the articles above mentioned, attention was directed to the several reasons for regarding arthritis and rheumatoid conditions

as referable to some disturbance in certain phases of the local or systemic oxidative metabolism, possibly involving the circulating blood. Since then, observations have been conducted in a number of directions which have given a somewhat different slant to the course of experimental work without changing its basal nature and purposes.

By way of résumé, it may be mentioned that the studies in the army above referred to showed normal values for nitrogen, calcium and fats in the fasting blood, a slight lag in the elimination of salt and water, a slightly lowered basal metabolism in 20 per cent of the cases studied and a definitely lowered sugar tolerance. This lowered sugar tolerance was most marked in general in the worst cases of arthritis, was definitely improved in convalescent groups and could be seen to return toward normal in many individual cases as they convalesced and recovered. This return to normal was independent of the type of successful therapy employed, but was most abrupt after the removal of causative infections. The lowered sugar tolerance was uninfluenced by such agents as the salicylates even in the presence of symptomatic improvement.

Observations recently reported[3] show that under the given conditions of the experiment, making brief use of a tourniquet, it was not infrequently possible to demonstrate a difference in the percentage oxygen saturation of the peripheral venous blood of arthritics as compared with normal persons. In some cases this difference, which consists in higher figures for the arthritics, was found to be very marked. It seemed at times to lessen with convalescence from the active process.

It was also shown that during the demonstration of a lowered sugar tolerance in arthritics, by the usual technic, there occurred a rise in the per cent saturation of the blood, which paralleled the arthritis rather closely, though absent in normal persons giving a normal sugar tolerance. The percentage saturation of oxygen very definitely rose even in some cases of arthritis with a normal sugar tolerance, so that in this respect also arthritics seemed to differ from normal individuals. Indeed, they could be grouped somewhat by this analysis alone without ascertaining the sugar figures. Experiments have shown, however, that the mechanism by which the respective concentrations of oxygen and sugar were brought about, are apparently different.[4]

While these general results were in keeping with the hypothesis on which these studies were based, attempts to relate them to chemical changes in the composition of the blood were not altogether successful; in fact, study of the blood gases in respect to the so-called dissociation curves for oxygen and carbon dioxide gave normal values and it became necessary to look in some other direction for the explanation.

As the result of certain recognized changes in the gaseous equilibria

of blood coming from a hyperemic part, and as the result of observations by Pemberton, Hendrix and Crouter[3] in collaboration with R. B. Osgood, that the percentage oxygen saturation rises markedly during an electric "bake" of the whole body it was believed that some solution might be found on the basis of changes in the rate of circulation. Experiments were therefore conducted by means of Stewart's hand calorimeters upon the rate of blood flow in arthritics and normal persons. While the results of these studies do not permit as yet of final conclusions, additional impetus was given to the view that the blood flow in arthritis, in the capillary circulation especially, may be below normal. Without citing here the evidence which makes up this view (*loc. cit.*), suffice it that this viewpoint lends itself to an explanation of a number of obscure factors in arthritis and also paves the way for further hypothesis.

It is of much interest for example, to note that the joints are structures whose blood supply is very small. Attention has been drawn to this in a previous communication.[1] The insertion of tendons, another favorite spot for arthritic disability, is also a point of poor blood supply. Furthermore, other structures whose blood supply depends upon extremely small bloodvessels are characteristically involved at times in arthritis, for example, in the painful condition known as irido-cyclitis. The frequency with which psoriasis may accompany arthritis is well known and here again it is noteworthy that the capillaries and nerve endings do not penetrate to the outer layer of the epidermis which is the chief seat of the lesion.[5]

By extending these considerations a little further it is of interest to note that in the muscles which constitute one of the chief sites of rheumatic disability, conditions are rather delicately balanced for the proper gas interchanges. Thus in tissues, such as the submaxillary glands, the tissue oxygen pressures approximate the venous oxygen pressure whereas in some others, including skeletal muscle, the oxygen pressure in the muscle is 25 mm. or less, *i. e.*, much below the capillary oxygen pressure. In the former, therefore the blood flow can be diminished to a considerable degree[6] without loss of oxygen to the tissue, but in the latter it cannot. In the same connection Krogh has shown[7] that the oxygen pressure in resting muscles is sometimes at least very low, but in working muscles it approximates that of the blood. Reference will be made later to the significance of these facts.

Some interesting collateral information can be adduced from the results of the expedition of Barcroft and his collaborators to the Andes for the purpose of studying the respiratory functions of the blood at great altitudes.[8] They observed among other points, that the condition of sore muscles popularly known as "charley horse," which arises more easily in the arthritic than in normals, followed

a smaller amount of exercise than is the case at low levels and they also noted that acclimatization was frequently accompanied by an enlargement of the ends of the fingers suggesting the condition known as hypertrophic pulmonary osteoarthropathy. It is well recognized that in certain forms of this condition the bony structure itself is increased.

Further study of the gaseous interchange under conditions known to benefit the arthritic process has opened other viewpoints of interest. Thus, Bazett and Haldane[9] have shown that normal subjects, immersed to the neck in a bath at 38° C. experience a rise in body temperature accompanied by hyperpnea, giddiness and faintness; they also noted a fall in the alveolar carbon dioxide a profuse alkaline sweat and a marked alkaline diuresis. This alkaline wave they compare to the changes occurring after voluntary forced breathing. Haggard has observed a drop in alveolar carbon dioxide with the increased temperature in a normal person immersed for twenty minutes in a bath at 40° C.[10] He observed a fall in the dissolved carbon dioxide but no change in the carbon-dioxide combining power of the blood, and deduces that the concentration of hydrogen ion (PH) of the blood must be presumably lowered. Pemberton, Hendrix and Crouter have observed[3] a similar fall in alveolar carbon dioxide in normal and arthritic persons subjected to "electric bakes;" and also a rise above normal in alveolar carbon dioxide after the bake in nearly every instance.

Studies of the sweat resulting from external heat or other stimuli have been conducted by very few workers and have given varying results, but the writer in collaboration with C. Y. Crouter[4] has observed the interesting fact that the sweat of the forehead of arthritics may occasionally reach a lower PH., (around 4.6) that is a greater acidity, than that of normal persons, and the further interesting fact that with both normals and arthritics there is a nearly invariable tendency for the sweat to become less acid or more alkaline as the "bake" or application of heat progresses. The only exceptions to this have been some cases of arthritis and one of scleroderma which remained acid throughout, at figures rather more extreme than any normals reached.

These facts can be correlated with the few known facts relating to the elimination of CO_2 through the sweat. According to Riffle *et al.*, excretion of acid is a function of skin and kidney[11] and according to Starling[12] at a temperature of 29° to 33° C., CO_2 output increases so that at 34° it is doubled and at 38.5° it may amount to as much as 1.2 gm. per hour (Schierbeck).

Recent studies by Cajori, Crouter and Pemberton have shown that if a rubber bag be placed around an arm during a general body bake the carbon-dioxide content of the bag rises parallel with the drop in the reaction of the sweat of the forehead or other

arm. The same workers* have also shown that there is an actual decrease in the hydrogen-ion concentration of the blood; that is, the blood becomes more alkaline as shown by the CO_2 absorption curves and by direct measurement of the PH by Cullen's method. In one case, the change was from a PH of 7.26 to 7.52. Koehler† has obtained similar results. The evidence is all in favor of the view that this change results from a loss of acid from the body, presumably CO_2 in part; somewhat through the sweat but more largely through the lungs and urine. The probability that the elimination of CO_2 plays a role in the benefit accruing from "bakes" has been suggested by Pemberton, Hendrix and Crouter[3] and unpublished work of Cajori, Crouter and Pemberton indicates that other acid substances are also eliminated through the sweat.[13]

It is obvious that some of the benefits of hot packs and sweats in conditions accompanied by an acidosis, such as nephritis, is referable to the loss of acid and to the alkalosis induced.

An important corollary can be drawn here as to the common denominator between the beneficial effects of external heat in arthritis and the benefits following exercise, and to a lesser degree massage. The periods of greatest malaise of the arthritic are following rest (sleep) in the early morning hours (4 to 5 A.M.), at which time the body temperature is lowest. The clinical state of the patient generally improves as the day wears on and toward 6 to 7 P.M. opposite conditions prevail, accompanied by parallel oscillations of the metabolic rate as shown by the elimination of carbon dioxide. Exercise in general is of benefit to rheumatoid conditions and is accompanied by a complex train of events which cannot be detailed here. The increased ventilation of CO_2 and the increased blood flow which accompany it, however, are probably analogous to those resulting from bakes. It is important to note that the transport of CO_2 is effected mainly by the cells, probably by the hemoglobin.[14] The content of blood CO_2 also depends largely upon its production in the body and this fact is to be borne in mind when considering later the beneficial consequences of low caloric diets.

It is well recognized that among the chief symptoms of arthritis are the absorption and deposition of bony tissue, which constitute an expression in the osseous structures of a process which operates in many other and possibly all tissues. There is not a little precise data available here. The suggestive work of Allison and Brooks,[15] has shown in dogs that non-use through nerve section may bring about a loss of more than 25 per cent of the mineral constituents of the bones in twenty-four days, due to a loss of the bone matrix rather than to a change in its composition. The condition induced is obviously one of metabolic inactivity, and, by the same token,

* Jour. Bio. Chem., 1923, **57**, 217.
† Arch. Int. Med., 1923, **31**, 590.

Lipschutz and Audova,[16] have reached the conclusion that atrophy of muscle following section of tendon may be nearly as great as that following section of the nerve supply and that the inactivity which follows, plays a decisive part in determining the atrophy. In line with these observations is the evidence that normal ossification and pathological calcification depend upon physico-chemical factors and variations in CO_2 concentration.[17] It would appear that bony overgrowth does not essentially differ from normal bone and it is logical therefore to regard most forms of rarefication and deposition as the result of changes in the intensity of local metabolic processes rather than of the introduction of new mechanisms. It is to be recognized of course that the various normal factors concerned may also vary in their relation one to another.

There are in the above experimentally ascertained facts ample data with which to attempt explanation of the mechanism producing the bony changes in arthritis. The evidence is at least suggestive that something interferes with the utilization of oxygen or its removal from the peripheral blood and on the basis of the premises already outlined the most likely explanation at present lies in some disturbance of the capillary or finer vascular control. The result is comparable to some of the effects produced at altitudes under conditions of anoxemia. Thus Schneider and Gregg and others have directed attention to the frequency, under such conditions, of fatigue and headache which are among the most frequent concomitants of the rheumatic syndrome. The interesting observations of Barcroft *et al.*, on muscle fatigue and stiffness have already been cited. Until evidence to the contary is forthcoming, one can believe that absorption and deposition of bony tissue are partly functions of changes in the gas equilibria at the part concerned. There might be little or no systemic evidence, in terms of changes in the end-metabolism, from such minute disturbances in the gas equilibria. These would be restored to normal when the blood from the part had passed beyond the zone of involvement to the more actively circulating current. It is at all events clear that we are dealing here with true chemical processes and analysis shows that the radicals of CO_2 and P_2O_5 play much of their usual important role in the bony metabolism.

It is indeed not necessary to postulate the presence of products of anoxemia such as the α-hydroxy acids although these may also be present. The formation of acids at the anoxemic centers of big infarcts during autolysis together with their neutralization at the pheriphery by the blood plasma have long since been recognized as established processes.[18] It is of the highest importance to note that, in contrast with the circulating blood, the fixed tissues cannot make use of the regulation of CO_2 content by pulmonary ventilation. Such fluids as the synovial are similarly handicapped because of the absence of cells and it has been shown that lymph becomes acid more readily than does the blood, for the same reason.

The suggestive researches of Jacobs[19] on the toxic and penetrating qualities of CO_2 in plants, even in alkaline solution, form the basis of much interesting speculation and experiment along this line and deserve consideration in relation to animal physiology. For further development of the problem of local tissue acidosis, however, and the chemistry concerned the reader is referred to the work of Schade, Neukirk and Halpert.[20]

The influence of "focal infection," brought about frequently by the action of streptococci upon surrounding tissues, finds some acceptable explanation along these lines, in the researches of Hoover, Rich and others. As above mentioned these workers have demonstrated the effect on the capillary circulation of a variety of substances resulting from proteolysis of which histamine is a type. Some interesting recent work of Manwaring and Boyd has shown that the effect of some bacterial toxins upon the capillary endothelium of the perfused heart is to produce marked edema and hemorrhage of the myocardium, dilatation of the tissue spaces, and the extravasation of numerous red blood cells.[21]

As already remarked, the sum total of these processes, however, is usually small and it is probably for this reason that so little disturbance is observed in determinations of the end metabolism; Cecil, DuBois *et al.*[22] observed a normal metabolic rate and normal rate of utilization of ingested carbohydrate in a series of 4 arthritics studied by them. The writer in collaboration with E. H. Tompkins observed a slight reduction in the metabolism of 20 per cent of 29 arthritic soldiers studied in the army. Marked disturbance are necessary before they show themselves in summation figures and it is clear on many counts that we must learn to think in terms of local acidosis and local departures from normal metabolism. Putting aside such metabolic changes of a more or less well-known nature in the smaller structures, there are also many unknown links in the chain of intermediary metabolism, interruption of which might be unrecognizable in end metabolic figures.

It is possible that some of the proliferation of tissues such as the pannus which covers the joint cartilage in the "proliferative" form of arthritis of Nichols and Richardson is in part a compensatory phenomenon seeking to vascularize the affected region with the aim of supplying adequate nutrition. By the same token, it is conceivable that the formation of fibrous tissue so frequently seen in arthritis is an expression of the same principle and indeed, this thought may be further extended to include the formation of fibrous tissue in some widespread pathological processes.

In addition to the disturbances in the local chemistry at a given site, inaugurated in a more or less mechanical way by changes in the smaller vascular channels, it is obvious that alterations in the nature of the blood passing through these channels may further

profoundly modify the situation one way or another. Thus, anemia is a sequel of chronic arthritis which tends greatly to aggravate the disease process. The corollary of this, however, is fortunately of clinical value and some of the most marked improvements in arthritis occur during the period when a secondary anemia is yielding to the influence of such an agent as arsenic. The heightened nitrogenous interchange and increased metabolism which result, contribute to this end, but one factor seems clearly to be the regeneration of red cells and the increase in hemoglobin. Partial proof of this is seen in the fact that improvement frequently ceases when the blood count has been brought up to normal or nearly so. The writer has seen many instances of this.

Following this thought and anticipating somewhat consideration of the influence of climate, etc., it may be said that the subacute arthritic frequently experiences an abrupt and somewhat striking improvement in passing from low to moderately high altitudes. It is well recognized by physiologists that there are two forms of adaptation to high altitudes. In the former, there is an almost immediate increase in the red cell and hemoglobin count, which is limited in degree and duration. It may last many days, however, and it is believed that during this period there are brought into circulation many red cells which had been more or less out of the active circulation. In the latter form of adaptation on the other hand, there occurs after a more prolonged stay at altitude a more lasting increase in hemoglobin and red cells, which is a direct function of the degree of altitude and the duration of exposure to it. There is also a marked increase in the percentage of young red blood cells. It is of interest to observe that the arthritic may undergo an exacerbation of his symptoms if he be transported abruptly to considerable altitude, but after acclimatization the change in the blood count is accompanied by a return to his usual clinical condition and sometimes by a betterment in his symptoms which may last for some time after reaching lower levels.

There are some other features of the blood count which will bear mention at this point, although properly belonging under the question of diet which will be taken up later. The injection of nonspecific protein and killed bacteria, which recently had quite a vogue, is apparently now regarded by Miller and by Snyder, (personal communications) who have probably had the largest experience with it, as of value chiefly in the acute or subacute cases and to a limited degree. Attention has been called in a previous article,[2] to the mechanism probably operative, but another factor to which benefit has been ascribed is the increase in polymorphonuclear cells. In contrast to this, the improvement which follows the institution of a low caloric diet in suitable cases is generally accompanied by a more or less pronounced relative lymphocytosis. That this increase is the concomitant of a low diet *per se*, is further

indicated by the studies of Benedict[23] who showed that among a squad of men living upon 1950 calories, the leukocytes remained normal but the lymphocytes were increased. There is definite evidence in this that improvement is not incompatible with an increase in the percentage of lymphocytes without change in the polymorphonuclears. It also militates against the view that the increase in polymorphonuclears is the prime factor in the benefit which occasionally follows non-specific protein therapy. It may be remarked that the increase in the blood count at moderately high altitudes which is sometimes accompanied by improvement in the arthritic process apparently chiefly or solely concerns the red cells and hemoglobin.

Attention has been called in previous publications[24] to the unquestionable benefits which follow the use of a restricted dietary in appropriate cases. These findings have recently been corroborated on a large scale by Fletcher[25] and also by others.

Perhaps one of the most useful purposes served by this form of treatment has been to afford a different visual angle and therefore another approach to the problem of arthritis. It has been pointed out elsewhere[1] that there must be recognized in arthritis two distinct groups of factors having influence, namely, the causative factors of exposure, various kinds of infection, intestinal malfunction, etc., relief of which may or may not cure the disease, and second, the various agents, such as heat, arsenic, radium, exercise, massage, sweats, etc., which have a distinct influence on the local or systemic metabolism. These last may operate even in the presence of the causative factor, they are quite independent of it, they produce their results in somewhat differing ways and they indubitably reflect part of the pathology concerned.

In line with the thought advanced earlier in this paper, it is important to note that nearly all measures of benefit *per se* in arthritis and rheumatism depend upon an increased local or systemic metabolism or upon an increased local or systemic blood flow. Demonstration of the influence of external physical stimuli upon the capillary circulation as shown by the studies of Krogh *et al.*, is of great assistance in enabling us better to understand the *rationale* of such measures as massage and external heat. The work of Carrier in this connection is particularly pertinent.[26] These considerations also add weight to the view here suggested that at least part of the pathology of arthritis is referable to disturbance in the finer vascular mechanism and blood flow.

It can be said with reasonable probability, however, that when a low calory diet proves of benefit, it does so on one hand by virtue of a reduction of some of the products of intestinal malfunction, causative of certain types of arthritis, and on the other hand by virtue of the lowered metabolic burden to be borne either in a systemic sense or locally at different sites. A lowering or adjust-

ment of this metabolic burden is the natural corollary of measures to hasten and improve the metabolic processes concerned, and often has brilliant results. As far as this phase of the question is concerned dietetic therapy has much of the limitation of any method which caters to a weakened function and should be used with a balanced appreciation of both sides of the equation.

In some recent studies by Pemberton and Crouter[4] observations were conducted upon the hydrogen-ion concentration of the feces in a number of cases of normal individuals and arthritics, the latter of whom included cases convalescing upon dietary lines. The hydrogen-ion concentration, however, ran very consistently between 6.4 and 7.4 for all classes of cases, and it could not be determined that subjects convalescing upon a diet gave figures different from those still ill or from normal subjects. So far therefore as the reaction of the feces can reflect the reaction of the intestinal tract, the evidence is against the view that changes in the hydrogen-ion concentration following reduction in the diet, chiefly of carbohydrate, constitute the factors of value.

Another interesting point in connection with the influence of diet is to be found in the betterment which some subjects experience, when eating an unrestricted diet, immediately following the ingestion of food. This effect is most marked in the early morning hours, their worst period. It has been shown that an immediate influence of food is markedly to increase the rate of blood flow in at least the peripheral circulation and Pemberton, Hendrix and Crouter[3] have shown that this influence is well marked in arthritis. Not only the arthritic disability *per se* but also muscular stiffness and the systemic fatigue and mental habitude of the arthritic may be markedly the momentarily influenced for the better. Thus the effect of coffee in the morning is sometimes temporarily striking as many arthritics can testify.

It is important to stress again the point previously mentioned[1] that after the inauguration of arthritis from such causes as focal infection or prolonged exposure there may occur a more or less chronic dislocation of physiology such that removal of the cause in late cases is no longer adequate to bring about recovery. In such instances other factors, within the economy, which would be at other times harmless, may operate to perpetuate the condition already outlined. Some of the "intestinal" forms of arthritis apparently rise *sui generis* but it seems probably that some of them also arise in the manner just mentioned, and appreciation of the train of factors concerned is sometimes necessary before important improvement can occur. It is pertinent to call attention here to the suggestive work of Bodine,[27] of Child[28] and of Hyman[29] who have shown in general that in certain lower forms of life the influence of fasting tends toward an increase of metabolism per kilogram and a rejuvenescence as regards the rate of oxidation.

The infrequency of arthritis or rheumatism in the course of severe diabetes has already been mentioned.[1] Since then, the courtesy of a few colleagues at scattered points and in medical audiences has called to the writers' attention a few cases in which the two processes were combined in mild degree, but instances of active and sustained arthritis in the course of severe diabetes are yet to be encountered. Information bearing upon any such cases would be appreciated by the writer.

One of the most interesting consequences of the application of the above hypothesis to the problem of arthritic disability is the explanation which is afforded of the influence of climate and weather upon the disease. Perhaps nothing is more firmly ingrained in the mind of the profession, as well as the laity, than that rheumatic symptoms sometimes undergo exacerbation and amelioration more or less coincident with certain outstanding changes in the weather. The writer has for some years kept a series of charts in which the attempt has been made to correlate these changes in the clinical condition of patients with fluctuations in the temperature, humidity, barometer and certain other factors. Observations are still pending but it can be said that there seems to be no constant single factor accompanying these changes. Increased humidity, a rising thermometer, a marked fall in the barometric pressure may all have their influence. It has long been taught in text-books that the metabolic rate in man remains practically constant because of the environment created by his clothing. It has been shown, however, that the metabolism of men at work in Africa is 10 per cent less than that of the same men at work in Berlin.[30] Furthermore, Ash and Hill[31] found that cool out-of-door conditions raise the basal metabolism even in the absence of shivering. It seems probable that the distinct exacerbations of arthritis which may accompany a rise in temperature are partly due to the tendency toward less intense metabolism. There is another factor which operates here, however, and that is the vapor tension which increases with the rise in temperature. It is of interest to note in this connection that there is a distinct vernal increase in the incidence of arthritic conditions. The writer has observed this for some eight years or more and Lambert[32] has also called attention to it in his analysis of the records of Bellevue Hospital, New York. Study of the records of the U. S. Weather Bureau[33] brings out the fact that the only discoverable constant operating in nearly all parts of the country, aside from the rise in temperature, is the so-called "march of the vapor tension" which begins in February and reaches its highest value in summer (July), corresponding almost precisely to the period of increased rheumatoid disability as viewed by long range perspective. The significance of this factor in its entirety remains to be worked out, though certain probable effects are obvious. Part of the benefit from moderate altitude may arise from the lower vapor pressure obtaining there.

On the basis of the pathology outlined, it is obvious also that the effect, upon a part, of exposure, following lying on cold stone or exposure of a wet surface to wind, finds explanation in the local circulatory changes which ensue. Finally, if the role of the circulation is postulated through either its vascular control or chemical make-up, it follows that changes in the barometric pressure probably have influence pro or con in the performance of the respiratory functions and in certain other respects. The influence of the weather on metabolism is further to be seen in the interesting figures arrived at by Murlin and his co-workers.[34] They observed that the winter ration of the U. S. troops in France contained over 5000 calories per man daily and that the total daily consumption of food per man averaged 3633 calories. Each man required approximately 400 more calories daily during the period October to March than during the remainder of the year. The period of lessened requirement and hence presumably of lessened metabolism corresponds almost exactly with the increased incidence of arthritis as above noted.

Theoretical considerations suggest and practical experience has shown that the climatological conditions best suited to the arthritic are those characterized by a reasonable degree of altitude of a thousand feet or so, a dry soil and a dry atmosphere. The benefits accrue chiefly after a visit to such regions and it is not to be supposed that people living under such circumstances are necessarily free from arthritis; indeed, the writer has had several patients from Arizona whose trouble originated in regions where the above conditions obtained and where the subjects had lived for years. In borderland cases, however, and those "hanging fire" the influence from these factors may have large importance.

For some years the Boston school of Orthopedists, particularly Goldthwaite, Osgood and their co-workers have advocated with success in certain types of cases, postural and active exercises of various sorts. It is obvious that any defect in the circulatory conditions as above outlined would be aggravated by relative stasis of the blood stream elsewhere or by protracted congestion of the viscera from malfunction, malposition or ptosis and it seems probable that at least part of the benefit accruing from these valuable measures finds its explanation here. The hyper-ventilation recommended probably also finds part of its justification along these lines.

There are many other facts in relation to the problem of arthritis and rheumatoid disabilities which allow of extending the usual visual angle and also afford leads for investigative attack. Space will not permit, however, of mentioning them here.

It was stated at the outset that no suggestion of finality was to be attributed to the outline of the pathology of arthritis herewith presented. The basis for this outline is to be found in many

established facts and in many suggested facts some of which are now the subject of investigation. It is obvious that as further studies substantiate or disprove the various tentative conclusions reached, any hypothesis seeking to visualize the subject as a whole will be subject to such modifications as are necessary in the attempted solution of any complex problem. It is hoped to make such studies and modifications the subject of later contributions.

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THE OCCURRENCE OF FEVER IN MALIGNANT DISEASE.

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Fever as a symptom of malignant disease has long been recognized and in fact occupied a prominent place in the writings of a generation ago. Frequent mention was made and considerable emphasis laid on fever in abdominal neoplasms by writers in the eighties and nineties but in later years this symptom has receded into the background, overshadowed, like many another purely clinical observation by the more spectacular findings of the laboratory. That a prolonged and marked hyperpyrexia can exist with uncomplicated cancer is a possibility that well nigh has been forgotten by medical men of today. As proof of this, witness the fact that in two of the most popular and recent systems of medicine no mention is made of fever occurring with cancer of the stomach. The further back one goes in the text-books and literature the more is reference to this point found.

The most comprehensive article is the statistical one of Max Freudweiler[1] embracing 475 carcinoma cases in the Zürich Clinic from 1884 to 1897. Over one-half these cancers were gastric and all but 40 were in the digestive tract. The occurrence of fever in all uncomplicated cases was 24.6 per cent and varied from 45 per cent of the liver and gall-bladder cases to 21 per cent of the pharynx and esophagus.

Naturally most of the statistical work has been done on carcinoma of the stomach. Osler and McCrae[2] in their clinical study of 150 cases of cancer of the stomach give fever as occurring in 49 per cent and Friedenwald[3] in a similar study found 43 per cent febrile. In 18 per cent of these febrile cases of Friedenwald's the fever ran through the entire course of the disease, in 25 per cent it occurred during the first six months, and in 74 per cent the last six months. Smithies and Ochsner[4] quote the Fenwicks as stating that approximately one-third of gastric cancer patients have elevations in temperature during some portion of the disease, and give their own figures as 15 per cent of 79 cases.

Besides this data on stomach growths, Musser[5] found that 18 out of 100 cases of cancer of the gall-bladder, and 7 out of 18 cases of biliary tract cancer had fever at some time or other, but felt that in all it was due to the complication of inflammation of the tracts, peritonitis or ulceration. As mentioned above, Freudweiler found that 45 per cent of 38 similar cases had fever.

A review of the subject and one of the very few papers dealing

with it in the last twenty years, is by Pedrini[6] who feels that two types of neoplastic fever should be distinguished—one due entirely to the growth and the other due to some pathological complication. He felt that cancer of the liver and pleura were more apt to be associated with fever than were growths of other organs.

A number of isolated but striking instances of neoplastic fever have been recorded, a few of which will bear mention: James Finlayson[7] in 1888 wrote a clinical note on the "Occurrence of Pyrexia, Shiverings and Pyemia in Cases of Malignant Disease," detailing six out of fourteen instances of malignant disease of the abdominal organs where fever occupied such a prominent place in the symptomatology that in several it was thought to be due to abscess and the tumor mass explored for pus. Marsh[8] found high fever with sarcoma of the kidney in a child, aged nine years, and again in a sarcoma of the femur in a boy of the same age, and adds that "such examples will serve to show that in doubtful cases a high temperature cannot be relied on to prove that a disease is inflammatory rather than malignant." Karsner[9] reported a carcinoma of the rectum in a girl, aged ten years, with fever considered due to a tuberculous peritonitis, and an adenocarcinoma of the liver in a girl, aged eleven years, with fever diagnosed as due to an acute endocarditis.

The significance of fever of varying types accompanying cancer has been noted mostly in the German literature, and they in particular stress the intermittent variety. Wunderlich[10] doubtless was the first, as in 1856 he observed that the fever may be intermittent in character and felt that once it ensued the course of the disease was apt to be very rapid. Libert[11] described a "light and hectic" carcinomatous fever, but to Hampeln[12] of Riga should belong the credit for having pointed out the clinical fact that a high septic intermittent fever with chills and sweats, lasting over long periods and simulating malaria, might be caused by carcinoma. All of his cases were in cancer of the stomach. Although his fever curves were not the typical Pel-Ebstein "Rückfallsfieber," his first observation of 2 cases antedated Pel's paper by one year and Ebstein's by two. Later Anker,[13] Bührig[14] and Kobler[15] reported other intances of this.

Freudweiler in his study divides his material into four classes according to the type of fever. The smallest number, 6 per cent of the febrile, or 1.5 per cent of the whole 475, had a continuous fever, with a diurnal variation of not more than one degree Centigrade. The next infrequent were the malaria-like paroxysms often accompanied by chills and recurring with fair regularity. Fourteen and a half of the febrile or 3.6 per cent of the whole, were of this type. Much more common were occasional rises lasting no longer than three days, and comprising 38.5 per cent of the febrile or 9.3 per cent of all. Most common of all was a remittent or intermittent fever.

This was the predominant type and was present in 41 per cent of the fever cases and 10.1 per cent of all the cancers. His findings are based on 117 instances where he felt conclusively that the fever was due to the cancer alone. Seventy-two others of the 475 showed fever but were not used, since in these other causes were present sufficient to give fever.

There has been considerable speculation as to the cause of the fever and its lack of consistency. Undoubtedly there is a rare but true neoplastic fever but more commonly it seems due to the necrosis and ulceration in the growth. Some hold that it is more frequent in those cases showing extensive ulceration and widespread metastases, although Osler and McCrae felt from the autopsies in their stomach series that these factors made little difference. Freudweiler states that in 64 autopsies on febrile cases, 50 were ulcerated and 14 not.

TABLE I.—DISTRIBUTION OF CASES AND PERIODS OF OBSERVATION.

Organ.	Cases.	Total days in hospital.	Average number of days in hospital.
Stomach	74	2330	31.5
Esophagus	16	644	40.2
Colon and rectum	19	992	52.1
Liver, etc.	23	850	36.9
Lung and pleura	5	267	53.4
Breast	21	923	44.0
Uterus	41	1052	25.6
Head and neck	32	1338	41.8
Prostate	7	240	34.2
Total	238	8636	36.0

The patients comprising the present study were seen on the University of California service of the San Francisco Hospital between July, 1917, and July, 1922. No questionable cases are included and the majority have been proven by autopsy or tissue examination at operation, although in a minority the diagnosis has been made on clinical evidence alone. Two hundred and thirty-eight cases form the basis of the report, with what might be termed "medical" or internal malignancy making up the greater number. The proportion of cases in the organs involved is shown in Table I. In this and the following tables the viscera are grouped together in nine classes according to the site of origin of the growth. The liver group consists of primary carcinomata of the liver, bile ducts, gall-bladder as well as pancreas. The head and neck group includes those cancers arising in nasopharynx, parotid, jaw, tongue and larynx. No cognizance is taken in this arrangement of metastases; if a growth arose in the stomach but metastasized into the liver and lung, it was classified only under stomach and not under the other two. In Table I is shown also the number of hospital days' residence with the averages for each group. The extremes ran from one to two

hundred and thirty-five days, but only five were in less than forty-eight hours.

In going over the records the point under scrutiny was the question of fever. Temperatures were taken in Fahrenheit, at least twice a day and frequently oftener. Anything over 99° by mouth or 100° by rectum was considered a fever, the rise for the first forty-eight hours after operation and the agonal rise the twenty-four hours preceding death being excluded in the calculations. In 127 cases fever occurred at some time during the hospital stay, but in 36 of these it was definitely due to some obvious cause and not the growth itself. The most common of these were postoperative complications, reactions following radium treatment, pneumonias and other intercurrent infections. The occurrence of these complicating fevers was highest in the esophageal carcinomata and was due to lung and pleural infections from ulceration into the respiratory tract. In 91 instances, or 38.2 per cent of the entire number, fever occurred from no cause other than the neoplasm itself, as far as could be determined, and it is these cases that are under analysis and discussion. One hundred and eleven or 46.4 per cent showed no fever at any time.

TABLE II.—OCCURRENCE OF FEVER.

Organ.	Number of cases.	Afebrile:		Fever not due to complications:		Fever due to obvious complications:	
		No.	Per cent.	No.	Per cent.	No.	Per cent.
Stomach	74	42	56.8	25	33.8	7	9.4
Esophagus	16	7	43.7	4	25.0	5	31.3
Colon and rectum	19	10	52.6	7	36.9	2	10.5
Liver, etc.	23	9	39.1	12	52.1	2	8.8
Lung and pleura	5	2	40.0	3	60.0	0	0
Breast	21	9	42.9	7	33.3	5	23.8
Uterus	41	18	43.9	15	36.6	8	19.5
Head and neck	32	10	31.2	16	50.0	6	18.8
Prostate	7	4	57.1	2	28.6	1	14.3
Total	238	111	46.7	91	38.2	36	15.1

In Table II are shown the figures for the several groups. It will be noticed that carcinoma of the lung and pleura and of the liver and bile passages carries with it the highest percentage of fever, a fact in agreement with Freudweiler and Pedrini. Cancer occurring in the parts about the neck and throat has likewise a high incidence of fever, possibly due to the large percentage of metastases in this group. The occurrence of fever in the other groups, comprising three-fourths of the entire number, falls in a fairly close range between 25 per cent and 36 per cent, averaging roughly 33 per cent and coinciding fairly well with the figure of Freudweiler's. One observation, frequently made, was the tendency of the temperature to become subnormal the last week or so of life, notwithstanding complications that ordinarily would give rise to fever. On several occasions a purulent peritonitis was found post mortem, that gave no

sign of its existence in the way of increase in temperature or pulse rate.

In considering the type of fever some difficulty was encountered in making a practical classification. Finally three arbitrary divisions were made: isolated rises not lasting more than twenty-four hours, remittent febrile attacks lasting from two days to two weeks with normal periods between, and a prolonged, either continuous or septic fever, persisting for weeks and dominating the clinical picture as a major symptom. The figures are shown in Table III. Isolated rises are by far the most frequent and amount to 60 out of 91, or 65.9 per cent of all febrile cases. The remittent variety comes next with 24 out of 91, or 26.4 per cent, while prolonged fevers are the rarest of all, amounting to 7.7 per cent. This last type is the most interesting and was encountered only 7 times—in 3 stomach cancers, and 1 each of rectum, liver, lung and uterus. Three of these have been reported in detail in a previous note.[16] These results may be expressed another way by saying that 25.2 per cent of all cases showed isolated rises in temperature, 10.1 per cent remittent, and 2.9 per cent continuous pyrexia.

TABLE III.—TYPES OF FEVER.

Organ.	Febrile cases. Number.	Isolated rises. Per cent.	Intermittent fever. Per cent.	Continuous or septic fever. Per cent.
Stomach	25	52.0	36.0	12.0
Esophagus	4	25.0	75.0	0
Colon and rectum	7	85.7	0	14.3
Liver, etc.	12	50.0	41.6	8.3
Lung and pleura	3	66.7	0	33.3
Breast	7	100.0	0	0
Uterus	15	73.3	20.0	6.7
Head and neck	16	75.0	25.0	0
Prostate	2	100.0	0	0
Total	91	65.9	26.4	7.7

TABLE IV.—FEVER IN METASTATIC CASES.

Organ.	All cases. Number.	Febrile cases. Per cent.	Metastatic cases. Number.	Metastatic cases, febrile. Per cent.
Stomach	74	33.8	44	34.0
Esophagus	16	25.0	6	33.3
Colon and rectum	19	36.9	8	62.5
Liver, etc.	23	52.1	13	53.8
Lung and pleura	5	60.0	3	66.6
Breast	21	33.3	19	31.6
Uterus	41	36.6	34	44.1
Head and neck	16	50.0	28	50.0
Prostate	7	28.6	2	50.0
Total	238	38.2	157	42.6

As noted above the relationship between metastases and fever often has been mentioned, and the cases were examined carefully as to this point. Again difficulty arose from the fact that but a limited number were available since the absence of metastases could be told only after a complete autopsy. Their presence however usually was readily determined, especially by operation, and those known to have had metastasizing growths are collected in Table IV. The incidence of fever in this group is compared with the incidence of fever in the entire lot and remarkable little discrepancy is found between the two. The only marked difference is in the colon-rectum group where the metastatic cases show a considerably higher proportion of fever than do the others. The prostatic growths were too few to be of any importance in the calculation. The non-metastatic group is very small and therefore hardly available for comparison, but is shown in Table V. With the exception of the single febrile carcinoma of the larynx, and the liver group, there is a slight reduction of the febrile percentages in the others.

TABLE V.—FEVER IN NON-METASTATIC CASES.

Organ.	All cases. Number.	Febrile cases. Per cent.	Non-metastatic cases. Number.	Non-metastatic cases, febrile. Per cent.
Stomach . . .	74	33.8	11	18.1
Colon and rectum	19	36.9	5	20.0
Liver, etc. . . .	23	52.1	5	60.0
Lung and pleura .	5	60.0	2	50.0
Head and neck .	16	50.0	1	100.0
Total . . .	238	38.2	23	33.3

The only statement permissible from these two sets of figures is that the presence of metastases does not seem to alter the occurrence of fever to any extent. This is in agreement with the conclusions of Osler and McCrae, who, from the autopsy cases of stomach carcinoma, felt that the presence of metastases had but little influence on temperature. It may be of interest to note here two remarkably contrasting cases of lung carcinoma. In one, with widespread metastases to lymph nodes, brain, adrenals and opposite lung, there was no fever during the thirty-five day hospital stay, while in the other, reported elsewhere, a carcinoma of the bronchus without metastases, gave rise to the most marked pyrexia of the entire series, the temperature not remaining normal for longer than forty-eight hours in the whole five months' observation.

The question of ulceration likewise is of interest on account of its bearing on fever. Numerous authors state that it predisposes to this, although here again Osler and McCrae found that it had no constant influence on stomach cancer. In the visceral cases the presence or absence of ulceration only could be determined by autopsy, but in the external growths of breast, uterus and neck it

was ascertained by inspection. One hundred and twenty-seven cases are available in this group and the total figures are given in Table VI in comparison with the figures for all cases. Again there is a remarkable agreement between the figures for all growths and the figures for the non-ulcerating growths. The main difference arises from the fact that ulcerations in a neoplasm are very apt to cause infection of adjacent parts with resulting fever, so that we see a considerable increase in the percentage of fevers arising from complications, with a corresponding decrease in the percentage of febrile ulcerating growths as compared to others. The presence of the ulceration in the growth itself increased the incidence of fever from 38 per cent to 45 per cent.

TABLE VI.—FEVER IN NON-ULCERATED AND ULCERATED CASES.

	Number.	Afebrile. Per cent.	Fever not due to complications. Per cent.	Fever due to obvious complications. Per cent.
All cases . . .	238	46.7	38.2	15.1
Non-ulcerated .	76	47.4	36.8	15.7
Ulcerated . . .	51	29.4	45.1	25.5

Summary.—The presence of fever of various types in malignant growths has long been known and more frequently was commented upon in the literature of a generation ago than at the present time.

A series of 238 cases of undoubted carcinomata of various organs was studied to determine the incidence of fever in malignant growths.

Thirty-eight and two-tenths of these showed fever, not due to any known complication, during some time of their hospital stay. The neoplasms of lung and liver gave the highest percentage of fever, while in the other organs fever incidence fell rather closely around 33 per cent. Fifteen and one-tenth per cent showed fever due to some obvious complication, the occurrence of these complications being greatest in cancer of the esophagus.

Isolated rises in temperature were by far the most frequent febrile phenomenon, comprising 65.9 per cent of all febrile cases and 25 per cent of all. Twenty-six and four-tenths per cent of fevers, or 10.1 per cent of the whole, were of the remittent type, and 7.7 per cent of fevers were of the long duration variety. In only 2.9 per cent of all cases did the hyperpyrexia approach a symptom of importance.

The occurrence of metastases did not appear to influence the incidence of fever.

The occurrence of ulceration did not increase the liability to fever except as it produced complicating infections in surrounding structures.

Conclusion.—In more than a third of the cases of carcinoma fever may be expected during some period of the illness, but its occurrence as a pronounced feature of the disease is an unusual finding.

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SCARLET FEVER AS A REACTION OF HYPERSENSITIVENESS TO STREPTOCOCCUS PROTEIN.*

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Outline.

I. Introduction.
II. A Comparative Study of the Clinical Features of Drug Allergy, Serum Allergy and Scarlet Fever.
III. A Study of the Relation of Streptococcus to Scarlet Fever.
IV. Experimental Investigation.
  (*a*) Methods.
  (*b*) Material.
  (*c*) Technic.
  (*d*) Results.
V. Discussion.
  (*a*) Epidemiological Observations.
  (*b*) Practical Applications.
VI. Summary.

I. Introduction. One of the outstanding, unsolved problems in preventive medicine is that which has to do with the exanthematous diseases of childhood and early adult life. Nothing has been proven as to the exact causes of these diseases and, with the excep-

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tion of vaccination against smallpox, we have as yet to develop adequate methods for their control.

From 1907 to 1917, while in the teaching of bacteriology and hygiene and the practice of clinical medicine, the study of several cases of food, drug and serum "idiosyncrasies," or "anaphylaxis," now better described as "hypersensitiveness," emphasized to the writer the similarity of the clinical signs and symptoms of these conditions to some of the common acute exanthematous diseases. From 1917 to 1921, as State Commissioner of Health in Maine, the further opportunity was presented to study several small outbreaks of scarlet fever, measles and smallpox; and again the impression was gained that one or all of the acute exanthemata might be special manifestations of specific protein hypersensitiveness. Because of the highly communicable nature of these diseases, it was at once conceived that the only logical theory to explain their etiology from the standpoint of hypersensitiveness must be one that assumes the proteins involved in sensitization and intoxication to be derived from the autolysis of various known or unknown microörganisms. A brief preliminary statement of this hypothesis was published by the writer[1] in 1917. A few suggestions of a similar nature have been noted in a recent study of the literature.[50]

II. A Comparative Study of the Clinical Features of Drug Allergy, Serum Allergy and Scarlet Fever. Before proceeding to a consideration of certain experiments to test such a theory, particularly as it regards scarlet fever, it will be of interest to compare the clinical characteristics of drug allergy and serum allergy (forms of allergic hypersensitiveness) with those of scarlet fever, in all three of which a suggestive parallelism is evident. At this time it is impossible to go into all of the details concerning the subject of hypersensitiveness to bacterial and other proteins or the subphenomena of anaphylaxis and allergy, a review of which may be obtained from such recent excellent summaries as that of Coca.[2] In passing, we would particularly emphasize again that hypersensitiveness may be caused by bacterial proteins as well as by proteins from other sources.

A study of Table I shows that these three conditions, drug allergy, serum allergy and scarlet fever, have strikingly similar clinical signs and symptoms which may appear singly or in combination. Each condition is characterized by an incubation period of variable length; a chill with headache and general malaise marks the onset in many cases; dyspnea is frequent in occurrence; more or less fever and vomiting are evident; skin eruptions, followed by more or less desquamation, are characteristic; fall in blood-pressure has been noted; eosinophilia is common to all three; local or general edema, lymph gland and joint involvement and albuminuria are frequently present; shock, loss of consciousness or a fatal termina-

TABLE I.—COMPARISON OF CHARACTERISTIC SIGNS AND SYMPTOMS OF DRUG ALLERGY, SERUM ALLERGY AND SCARLET FEVER.

Characteristic signs and symptoms.	Drug allergy.	Serum allergy.	Scarlet fever.
Incubation period	Variable, two hours to twenty days. Generally short	Variable, few hours to twenty-four days. Average ten to twelve days	Variable, two to four days. Some instances of ten to fourteen days average.
Chill	Frequent	Frequent	Frequent.
General malaise and headache	Frequent	Frequent	Frequent.
Dyspnea	Frequent	Frequent	Frequent.
Fever	Frequent; may reach 106° or more	Frequent; 106° or more	Common; usually high.
Vomiting	Frequent	Frequent	Frequent.
Angina	Absent; difference in "portal of entry" and primary lesion	Absent; difference in "portal of entry" and primary lesion	Common; throat and tonsils probable initial or primary lesion.
Skin eruption	Common; varies in character. Frequently "scarlatiniform." General over body. May first be local following hypodermic injection.	Common; first local around site of injection. Later generalized. Frequently "scarlatiniform."	Common; first local over front and sides of neck and on upper chest. Adjacent to portal of entry (throat or tonsils). Becomes general.
Skin desquamation	Fairly common, fine scales to large flakes or even casts of hands, etc.	Typical in some cases	Common.
Edema	Fairly common; local (face) or general	Fairly common; local (face) or general	Fairly common; local (throat or face) or general.
Eosinophilia	10 to 15 per cent increase in most cases	Cases reported, 10 to 14 per cent increase in experimental food allergy	As much as 20 per cent increase.
Lymph gland involvement	Frequent	Frequent	Frequent.
Joint involvement	Frequent	Frequent	Frequent.
Albuminuria	Frequent	Frequent	Frequent.
Fall of blood-pressure	Few cases reported	Cases reported	Frequent.
Shock and fatality	Occasional	Occasional	Frequent, in "malignant" type.
Protection	In some cases a "tolerance" is established	Common after recovery from "shock." Not always permanent	Common after recovery. Not always permanent.
Inheritance of susceptibility	Positive evidence in some cases	Positive evidence in some cases	Positive evidence in some cases.
Therapy	Condition improves on discontinuance of drug	Adrenalin and atropine of value	Adrenalin of value in severe cases. Atropine may lessen susceptibility.

tion at times occur; following recovery, or an establishment of tolerance, more or less protection at least temporarily is induced; in several instances hereditary susceptibility has been noted; therapeutic benefit has been derived from the same drugs. Regarding the signs and symptoms of hypersensitiveness in general, Coca[3] states that "They are uniform in any one species for various substances." On this basis the almost complete uniformity in the signs and symptoms of these three conditions in man is definitely suggestive that not only are drug allergy and serum allergy specific forms of hypersensitiveness but that scarlet fever also may be a manifestation of a specific hypersensitiveness. It must be admitted that a few authorities do not agree that so-called drug idiosyncrasies are based on conditions of hypersensitiveness. However, the hypothesis advanced by several of the most noteworthy investigators—that drug reactions may be based on an abnormal alteration of blood and tissue proteins by the chemical, thus *acting* as foreign protein to the injected animal or affected person—has much to commend it.

It would be without profit at this time to make a detailed study of all the above-mentioned signs and symptoms as they relate to each disease. It may, however, be said that no one sign or symptom is pathognomonic of any one of the three conditions. The signs and symptoms, as a whole, must be taken into consideration in reaching a diagnosis, and even then it is often very difficult to be positive as to the nature of the disease in question. Frequently the history must be relied upon to determine the possible taking of a drug, the injection of a serum or an exposure to scarlet fever or a septic infection. The one feature of the three conditions which seems, and which might logically be expected, to vary considerably in each is that of the portal of entry, or local primary reaction; in scarlet fever this apparently is in the mouth, throat or tonsils, giving rise to the typical angina and "strawberry" tongue, accompanied by the exanthem which first shows itself on the neck and upper chest, that is, in the immediate vicinity of the portal of entry. In so-called "traumatic scarlet fever" due to injuries, burns, etc., or "postoperative scarlet fever" the exanthem, as a rule, starts adjacent to the wound, burn or operation site; in "puerperal scarlet fever" the eruption first appears in the neighborhood of the generative organs, that is, on the lower abdomen and upper part of the thighs. If a drug or a serum is injected, and is followed by evidence of hypersensitiveness, the eruption usually appears first around or near the injection site. It is evident, therefore, that the history of the case, a knowledge of the local "portal of entry" and of the exact site of the primary lesion or reaction, and of the first local manifestation of the eruption are of chief importance in the differential diagnosis of these three conditions.

The most spectacular signs that may be present in drug allergy, serum allergy and scarlet fever, and which it might be well to consider a little more in detail, are found in the skin in the form of eruption and desquamation and in the blood in the form of eosinophilia. Drug and serum allergy may be accompanied by erythematous, urticarial, vesicular, macular, papular, hemorrhagic, morbilliform or scarlatiniform rashes, the latter two being particularly evident following certain drugs and also in serum allergy. Desquamation, or exfoliation of the skin, following a rash may be be present in all three of these conditions. It is a mistake to insist that desquamation alone is a pathognomonic sign of scarlet fever. Serum allergy, especially severe cases, may be followed by a certain amount of scaling of the skin, and very definite desquamation has been noted following the eruptions caused by such drugs as antipyrin, chloral hydrate, chloralamide, quinine, salicylic acid, copaiba, digitalis, mercury and morphia.

Pye-Smith[4] reports a case of a man who had taken 40-grain doses of chloralamide every night for twelve nights. On the thirteenth day a diffuse bright red scarlatiniform eruption appeared on the face and soon became general, including the mucous membranes. The temperature reached 103° F. The eruption lasted a week and was followed by a large, flaky desquamation. Stelwagon[5] reports a case of drug allergy following the taking of $\frac{1}{6}$ grain of quinine by mouth. A general scarlatiniform rash appeared and was followed by characteristic desquamation. In another case[6] of quinine allergy casts of the hands and feet were thrown off and exfoliation persisted for weeks. It has been shown[6] that desquamation also may follow copaiba eruptions, but only when the drug is continuously administered. In other words, the element of time as well as severity must be considered in explaining the causation of desquamation following various eruptions. In a case[6] of digitalis allergy an eruption was followed by desquamation in large flakes and complete shedding of hair and nails.

In drug allergy an eosinophilia to the extent of 10 to 15 per cent increase has been noted.[7] A definite eosinophilia has been found[8] also in experimentally produced food allergy in guinea-pigs. It has been demonstrated by others[9] to be present in cases of serum allergy. Berger[10] reports an eosinophilia occurring in breast-fed infants following the ingestion of a foreign protein, such as cows' milk. Herrick[11] was able to develop a notable eosinophilia in guinea-pigs by the intraperitoneal injection of an aqueous extract of ascaris lumbricoides and he believes the substance causing such an increase of eosinophils to be a protein. A marked increase in the number of eosinophils has been found associated with hay-fever, eczema, urticaria and asthma, due to protein sensitization, and with animal parasitic infestation. Clarke and Meyer[12] report an interesting case of hypersensitiveness

to silk in which the blood revealed 10.5 per cent eosinophils. Although we have no detailed information as to how it is brought about, the general opinion of the best authorities is that all of these instances of eosinophilia are associated with some form of specific hypersensitiveness. In fact, Schlecht[13] concludes that eosinophils have the special function to protect the body against the invasion of a foreign protein. The work of others, also, indicates that an increase in the percentage of eosinophil cells in the blood is evidence of sensitization to a protein, either by subcutaneous, intravenous or natural routes, such as through the mucous membrane. An important factor in such eosinophilia is that of the time element. As a rule, such increase of eosinophils takes place only after a variable period of time following the introduction of an alien protein or sensitizing agent, and though frequently persistent it may be only of short duration. It is usually a feature of the so-called posthypersensitive stage.

As Moschcowitz[14] states: "The relation of eosinophilia to anaphylaxis suggests, perhaps, that other diseases commonly associated with eosinophilia may be regarded as anaphylactic in nature." With this demonstrated relation of eosinophilia to hypersensitiveness in mind, it is at least very suggestive to find that an eosinophilia is rather characteristic of the later stages of scarlet fever. While the average percentage of eosinophils in the blood of a perfectly normal person may be from 2 to 4 per cent, Emerson[15] states in regard to the eosinophils that: "In scarlet fever these cells may vary from 8 to 15 per cent." Holt,[16] in describing the blood in scarlet fever, tells us that "During the first week the eosinophils are diminished; after the fifth or sixth day there is rapid increase in the eosinophils which attain their maximum, sometimes 20 per cent of the total leukocytes, between the fourteenth and twenty-first days. After the third week they gradually diminish."

III. A Study of the Relation of Streptococcus to Scarlet Fever. Without attempting to cite all of the literature and evidence for or against the etiological relation of the streptococcus, either as a special group or in general, to scarlet fever, the following statement of Bergé,[17] made in 1895, must be given serious consideration: "An imposing array of evidence points to the streptococcus in one of its virulent forms as the pathogenic agent of the disease." More recently Bliss[18] states that he has found hemolytic streptococci in 100 per cent of the throats of patients with scarlet fever during the first week of the disease, and that these organisms are present in the throat for an average period of from ten to twenty days. While no morphological or cultural characteristics have been demonstrated that seem to differentiate the hemolytic streptococcus associated with scarlet fever from other types of Streptococcus pyogenes, Bliss believes that from the standpoint of serological

reactions hemolytic streptococci found in scarlet fever throats may constitute a single biological group. Be this as it may, up to the present time the attitude of the "court" of scientific investigation has been that the streptococcus is "innocent" of being the cause of scarlet fever until "proven guilty," and convincing, final proof has not been forthcoming. Strong circumstantial evidence is at hand but it has not been considered sufficient. Many, if not most, of the authorities assume that some mysterious "advance agent" goes with or ahead of the streptococcus and prepares the way for the latter; in other words, that this agent—the supposed primary etiological factor—and the streptococcus are in symbiosis or "partnership." Why complicate the problem in this way until we have exhausted all the possibilities of the streptococcus, or its autolytic products alone, as the primary etiological factor in scarlet fever?

The chief arguments against the idea that streptococcus is the cause of scarlet fever may be enumerated as follows:

1. The inoculation of streptococcus into healthy individuals apparently has not caused the typical disease, scarlet fever.

2. Streptococcus infection does not, as a rule, confer an immunity to subsequent infection, while in most instances an attack of scarlet fever apparently does protect against subsequent attacks.

3. In cases of uncomplicated scarlet fever, in which death has occurred on the second or third day the blood and internal organs usually are found to be sterile.

In answer to the first argument, from the standpoint of our hypothesis, it may be said that in the comparatively few experiments in an attempt to cause scarlet fever in healthy individuals by inoculation with streptococcus, such persons may not have been hypersensitive to streptococcus protein and hence naturally would not show any evidence of an anaphylactic or allergic attack.

On the other hand, the injection of "prophylactic" streptococcus vaccine, made up of dead organisms, according to Gabritschewsky,[19] in from 10 to 15 per cent of his cases *has* resulted in a scarlatiniform eruption at the site of injection often followed by a general eruption, associated with fever and many of the other symptoms of typical scarlet fever. Kogan[20] obtained similar results in 9 out of 62 children following the administration of streptococcus vaccine. Krumweide's[21] assistant accidentally swallowed a suspension of streptococci. Two days later this assistant developed a sore throat followed by all the so-called classic symptoms of scarlet fever, including desquamation. There had been no known contact with a case of scarlet fever. Unless all of these instances were simply coincidental cases of scarlet fever (an unwarranted assumption) it must be admitted that scarlet fever, at least of a mild nature, *may be* and *has been* thus artificially produced in certain persons hypersensitive to streptococcus protein.

Regarding the second argument that streptococcus infection does not confer an immunity while scarlet fever usually does, it may be said that although the *infection* with streptococcus may not result in protection, *protein sensitization and intoxication* from the autolysis of this organism theoretically *should* result in more or less antianaphylactic protection, as is the case following recovery from acute attacks of anaphylactic or allergic shock or following experimentally produced bacterial hypersensitiveness.

This refractory state, or antianaphylaxis, is not necessarily permanent nor absolute. However, animals experimentally injected do not show the same degree of hypersensitiveness thereafter, symptoms if present being mild and rarely leading to a fatal result. Moreover, it is quite possible that in scarlet fever the protection following one attack may be more *apparent* than real. In other words, the power to react may have been changed to such an extent that subsequent attacks have such a short incubation period, and are so mild and "fleeting" in character, that their real nature is not evident. Such an accelerated or immediate reaction may be protective, and may depend on the original hypersensitiveness, just as a primary reaction or "take" follows the first successful vaccination against smallpox, while in a subsequent vaccination the incubation period may be much shortened and the clinical features lessened or apparently absent. On the other hand, relapses and second attacks of scarlet fever are not so very uncommon, indicating in such instances a possible continuance or return of a mild hypersensitiveness in this disease.

The fact that the blood or internal organs in cases of scarlet fever frequently are found to be sterile before or after death, even on the second or third day of the disease, may not necessarily weaken our theory. In fact this is what might be expected if scarlet fever is merely a manifestation of a streptococcus protein hypersensitiveness. Streptococci may remain localized in the throat or tonsils as the "primary lesion" or "portal of entry" in typical, uncomplicated scarlet fever, as suggested by Bergé;[17] or they may remain localized in the uterus (in puerperal scarlet fever), wounds (traumatic scarlet fever), operation sites (surgical scarlet fever), burns (scarlet fever following severe burns). Rosenau and Anderson[22] state that "When bacteria grow in the body they are dissolved by lytic agencies, and the foreign protein in the individual germ cells may sensitize the body and afterward poison it." From these local sites, or primary lesions, such as the throat or uterus, following the autolysis of streptococci, protein molecules may be absorbed in sufficient amount to give rise to typical signs and symptoms of scarlet fever in hypersensitive individuals. In other words, these local areas, portals of entry, or primary lesions, may be analogous to the local sites of experimental injection of various substances in the artificial production of anaphylaxis or

allergy. That these "extrafaucial" cases of scarlet fever are identical in general nature and etiology with typical cases of the the disease was formerly much doubted. However, many of the leading authorities have become convinced that the scarlatinoid eruptions following cutaneous burns, operations and the puerperium represent in reality the exanthem of scarlet fever. In fact, Schamberg[46] cites an interesting case in which a nurse contracted a typical case of scarlet fever from a boy whom she was nursing, this boy having developed the disease in connection with a severe burn on the face and arm. The child showed no characteristic signs in the throat or on the tongue.

Based on the above brief comparative study of the clinical signs and symptoms of drug allergy, serum allergy and scarlet fever and of the relation of streptococcus to scarlet fever, an account will now be given of certain experimental investigations.

IV. Experimental Investigation. A. METHODS. In this experimental investigation it was decided to make use of the ordinary cutaneous test to determine whether or not scarlet fever gives evidence of being a reaction of specific protein hypersensitiveness. Having in mind the very definite relation of the streptococcus to scarlet fever, as outlined previously, it seemed logical to test the sensitiveness of scarlet fever patients and normal controls to streptococcus protein.

In this procedure several factors must be kept in mind: (1) As suggested by Schloss,[8] in testing for allergy a negative cutaneous test is not always conclusive, and for various reasons. Such a negative test may be due to a lack of *skin* sensitization in certain individuals or to an occurrence of a temporary general desensitization of the body during or after an attack or treatment of protein sensitization. For example, Schloss demonstrated in infants showing an original positive cutaneous sensitization to egg and milk, that after marked signs and symptoms, including urticaria, had occurred (following ingestion of these proteins) the cutaneous reaction immediately disappeared for variable periods of time. In other words, the original cutaneous sensitiveness was destroyed by the general reaction. Our experiments and deductions herein noted are based primarily on these findings of Schloss. (2) Such cutaneous tests may vary considerably in intensity or grades of reaction and in the time interval after the test has been made. Thus, Longcope[23] found that in cases of urticaria or eczema due to protein sensitization the interval between the test and the skin reaction may be prolonged. He showed also that in such cases the skin reactions are not always obtained, in fact may be rare unless the intracutaneous method is used. Others have demonstrated, however, that the intracutaneous test may be non-specific in some cases. In fact, Walker[25] believes that the intradermal test is *too* delicate, if not actually non-specific, and he suggests

that the linear scratch cutaneous test probably is more reliable. In this work, therefore, it was decided to use only the linear and rotating scratch cutaneous tests. Based on the experiments of Schloss, it was considered necessary to keep in mind the fact that if scarlet fever is a reaction to a streptococcus protein hypersensitiveness, such tests on patients in various stages of scarlet fever might or probably would result in negative or, at most, weakly positive reactions, because of desensitization or antianaphylaxis, at least temporarily induced. It would then become necessary to determine if possible any later reappearance of hypersensitiveness and any change in degree or intensity of the same. Moreover, it would be of interest to note the relative sensitiveness to streptococcus protein of persons who have had scarlet fever at some time in the past compared with normal controls giving no history of the disease.

B. MATERIALS. Cases of scarlet fever, as well as individuals, giving both positive and negative past histories of the disease for controls, were put at my disposal by the Minneapolis General Hospital and the University of Minnesota Health Service, due acknowledgment of which is made later.

Bacterial proteins for the tests were obtained from H. K. Mulford Company in the form of so-called "Bacteria Dried." These are described by the Mulford Laboratories as "Proteins prepared from mass cultures of specific bacteria, killed, mixed, dried and ground to a fine powder. 'Bacteria Dried' are used in cutaneous tests to determine the sensitiveness of individuals to any one of the groups of bacteria, which, in many instances, have been found to be the cause of asthmatic symptoms and complications of pollen hay-fever."

As to the source of the streptococci used in the preparation of the so-called "Streptococcus Dried" it is stated[24] that they are "Mostly from hemolytic strains collected from various sources and contain streptococci isolated from scarlet fever throats." As to the method of killing these organisms, it is stated that "They are submerged in a tank of water in sealed bottles containing about 500 cc. These bottles are firmly held in an apparatus which revolves beneath the water, and the agitation insures that all organisms in the bottle are evenly heated. The temperature of the tank is 60° C. for one hour."

C. TECHNIC. 1. As a first group, experiments were tried on 35 patients in various stages of scarlet fever. Most of these patients were tested by a slight modification of the linear scratch cutaneous method recommended by Walker,[25] while a certain proportion were tested by the well-known rotating scarification method.

2. A second group of controls, made up of 48 persons not having the active disease, were tested by the linear scratch method. This group was further subdivided into two series: One made up of

31 persons, giving no history of scarlet fever, and the other consisting of 17 individuals who had had the disease at some time in the past. Since this linear scratch method gave a rather high percentage of positive reactions in these controls, it was not thought necessary to check them with other more delicate methods.

For the linear scratch tests, sharp, sterile sewing needles of average and uniform size were used. On the right upper forearm (after the usual cleansing) a superficial scratch $\frac{1}{4}$ inch long was made to serve as a control without streptococcus protein. On the left upper forearm (after like cleansing) a scratch of the same nature and size was made, and into the exuding lymph along this scratch was gently, but thoroughly, rubbed a quantity of dried streptococcus protein which could be held in the "eye" of the needle.

The rotating scarification or abrasive test consisted of two abrasions on the left forearm of the patient, made with a skin-borer following the cleaning of the skin. One of these denuded areas was left as a control, while into the other an amount of dried streptococcus protein, which could be carried in the "eye" of an average sized sterile needle, was gently but thoroughly rubbed.

In most cases the dried streptococcus protein alone was rubbed into the exuding lymph, covering the scratch or abrasion; in a few cases a drop of $\frac{N}{10}$ sodium hydrate was added. There seemed to be no difference in the results from this standpoint.

D. Results. The results of these tests were inspected at various hourly and daily intervals up to a week or more. Only positive and negative results are here reported. All cases of questionable or doubtful positive reaction are included as negative.

A positive reaction following the scratch cutaneous test in these experiments is one which consists of definite infiltration and elevation of the scratch and the immediately surrounding tissue, in some cases in the form of an elongated "wheal," together with a secondary areola of redness or erythema of irregular outline. This area of elevation and redness varies in diameter, but only those reactions are designated as positive in which the diameter is $\frac{1}{2}$ inch or more. In a few instances a very faint and narrow area of redness appeared about the scratch, but such were termed negative. All controls without protein were absolutely negative, while in most instances all tests with protein designated as negative were clearly negative; that is, nothing persisted except the original scratch line, unassociated with infiltration, elevation or a surrounding erythema. It was noted that when the test was made early in the disease, that is, during the first few days while a generalized scarlet fever eruption was present, the result was clearly negative. Questionable or doubtful positive reactions (designated as negative) appeared only in those cases tested during the last days of convalescence.

Positive reactions in the control individuals appeared in from four to eighteen hours, reached a point of maximum intensity in twenty-four to forty-eight hours, and then faded rapidly in three or four days, leaving little or no discoloration or scaling.

By reference to Table II it will be noted that out of 35 cases of scarlet fever, in various stages of the disease, tested with streptococcus protein by cutaneous methods no case developed a clearly positive reaction. All were negative, as were the controls without protein.

TABLE II.—CUTANEOUS SENSITIZATION TESTS WITH STREPTOCOCCUS PROTEIN ON 35 ACTIVE CASES OF SCARLET FEVER.

Case.	Sex.	Age.	Clinical diagnosis.	Duration of illness.	Method of test.	Protein used.	Result.	
							Protein test.	Control test.
V. B.	M.	19	Sc. fever	3 days	Scratch	Streptococcus	Negative	Negative.
L. A.	M.	18	"	1 "	"	"	"	"
F. C.	M.	17	"	3 "	"	"	"	"
D. L.	M.	7	"	8 "	"	"	"	"
B. N.	M.	8	"	8 "	"	"	"	"
M. F.	M.	4	"	7 "	"	"	"	"
L. A.	M.	7	"	5 "	"	"	"	"
G. S.	F.	29	"	15 "	"	"	"	"
E. W.	M.	33	"	6 "	"	"	"	"
I. H.	F.	26	"	24 "	"	"	"	"
D. E.	F.	30	"	25 "	Abrasive	"	"	"
A. L.	F.	26	"	29 "	"	"	"	"
M. B.	F.	18	"	16 "	"	"	"	"
H. P.	F.	18	"	6 "	"	"	"	"
F. F.	F.	13	"	19 "	"	"	"	"
L. A.	M.	7	"	13 "	"	"	"	"
M. F.	M.	4	"	15 "	"	"	"	"
B. N.	M.	8	"	16 "	"	"	"	"
D. B.	M.	7	"	16 "	"	"	"	"
S. R.	M.	9	"	16 "	Scratch	"	"	"
S. L.	F.	3	"	5 "	"	"	"	"
A. A.	M.	3	"	17 "	"	"	"	"
T. T.	M.	9	"	4 "	"	"	"	"
M. J.	F.	24	"	15 "	"	"	"	"
J. C.	M.	23	"	5 "	"	"	"	"
P. D.	F.	20	"	3 "	"	"	"	"
M. B.	F.	8	"	21 "	"	"	"	"
M. W.	F.	17	"	16 "	"	"	"	"
L. R.	M.	2	"	9 "	"	"	"	"
V. A.	M.	5	"	6 "	"	"	"	"
G. B.	M.	21	"	2 "	"	"	"	"
M. P.	F.	8	"	9 "	"	"	"	"
R. T.	F.	25	"	9 "	"	"	"	"
P. N.	M.	27	"	9 "	"	"	"	"
A. P.	F.	32	"	11 "	"	"	"	"

A study of Table III brings out the fact that of 17 persons giving a positive history of having had scarlet fever at some time

in the past, 7, or 41 per cent, showed a positive reaction, while 10 gave a negative reaction when tested with streptococcus protein by the scratch cutaneous method, all control tests without protein being negative.

TABLE III.—CUTANEOUS SENSITIZATION TESTS WITH STREPTOCOCCUS PROTEIN ON 17 INDIVIDUALS GIVING PAST HISTORY OF SCARLET FEVER.

Case.	Sex.	Age.	History scarlet fever.	Years since disease.	Method of test.	Protein used.	Results.	
							Protein test.	Control test.
A. O.	M.	23	Positive	1*	Scratch	Streptococcus	Negative	Negative.
V. S.	M.	17	"	1*	"	"	Positive	"
C. L.	M.	18	"	1*	"	"	Negative	"
M. W.	M.	20	"	1*	"	"	Positive	"
P. H.	M.	24	"	1*	"	"	Negative	"
A. R.	M.	17	"	1*	"	"	"	"
I. K.	M.	18	"	1*	"	"	Positive	"
C. K.	M.	18	"	1*	"	"	"	"
M. S.	M.	19	"	1*	"	"	Negative	"
P. B.	M.	17	"	1*	"	"	"	"
C. N.	M.	16	"	Several	"	"	Positive	"
M. S.	F.	25	"	"	"	"	Negative	"
M. G.	F.	27	"	"	"	"	Positive	"
A. V.	M.	21	"	"	"	"	Negative	"
F. D.	M.	22	"	"	"	"	Positive	"
B. H.	M.	22	"	"	"	"	Negative	"
P. R.	M.	18	"	"	"	"	"	"

* Cases thus marked had scarlet fever one year ago in the same epidemic.

A third group of persons, who gave no history of scarlet fever in the past, were tested and the results noted in Table IV. Out of 31 persons tested with streptococcus protein by the scratch cutaneous method, 19, or 61 per cent, showed a positive reaction and 12 a negative reaction. All controls were negative.

A general summary of these reactions is given in Table V, comparing the negative reactions in 35 active cases of scarlet fever with 41 per cent of positive reactions in 17 individuals who had scarlet fever at some time in the past (several of them within one year) and 61 per cent of positive reactions in 31 persons who never had the disease.

Is it not significant that all active cases of scarlet fever in these experiments showed a negative reaction, while normal controls, those not having the active disease, showed a rather high percentage of positive reactions? Schloss[8] states that "Sufficient evidence has accumulated to make it reasonably certain that a positive skin reaction in the presence of negative control tests is indicative that the patient is sensitive to the protein to which it

reacts." From this standpoint we may state that those apparently normal persons in our experiments who gave a positive reaction were sensitive to streptococcus protein, and it suggests that a certain percentage of all persons (either those who have had scarlet fever in the past or who have not had it) may be sensitive to this particular protein. It is of interest to note further

TABLE IV.—CUTANEOUS SENSITIZATION TESTS WITH STREPTOCOCCUS PROTEIN ON 31 INDIVIDUALS GIVING NO HISTORY OF SCARLET FEVER.

Case.	Sex.	Age.	History of scarlet fever.	Present condition.	Method of test.	Protein used.	Results.	
							Protein test.	Control test.
A. J.	M.	21	Negative	Normal	Scratch	Streptococcus	Negative	Negative.
C. N.	M.	19	"	"	"	"	Positive	"
R. O.	M.	16	"	"	"	"	Negative	"
R. W.	M.	17	"	"	"	"	"	"
R. C.	M.	19	"	"	"	"	Positive	"
M. T.	F.	20	"	"	"	"	"	"
M. O.	F.	21	"	"	"	"	"	"
A. F.	M.	17	"	"	"	"	Negative	"
L. K.	M.	17	"	"	"	"	Positive	"
C. W.	M.	17	"	"	"	"	Negative	"
F. S.	M.	20	"	"	"	"	Positive	"
N. U.	M.	16	"	"	"	"	"	"
L. B.	M.	18	"	"	"	"	"	"
H. J.	M.	17	"	"	"	"	"	"
F. W.	M.	19	"	"	"	"	Negative	"
D. L.	M.	16	"	"	"	"	Positive	"
W. D.	M.	19	"	"	"	"	"	"
L. C.	M.	20	"	"	"	"	Negative	"
D. G.	F.	21	"	"	"	"	"	"
R. P.	M.	20	"	"	"	"	Positive	"
V. T.	M.	19	"	"	"	"	"	"
W. O.	M.	26	"	"	"	"	"	"
R. W.	M.	23	"	"	"	"	"	"
S. F.	M.	18	"	"	"	"	"	"
W. J.	M.	20	"	"	"	"	Negative	"
H. J.	F.	22	"	"	"	"	Positive	"
L. F.	F.	18	"	"	"	"	Negative	"
M. R.	F.	19	"	"	"	"	"	"
M. S.	F.	24	"	"	"	"	Positive	"
D. A.	F.	18	"	"	"	"	Negative	"
R. B.	M.	18	"	"	"	"	Positive	"

TABLE V.—SUMMARY OF ALL CASES TESTED WITH STREPTOCOCCUS PROTEIN (35 CASES OF SCARLET FEVER AND 48 CONTROLS).

Nature of cases.	Number tested.	Number positive.	Number negative.	Per cent positive.
Cases of active scarlet fever . .	35	0	35	0
Individuals giving past history of scarlet fever	17	7	10	41
Individuals giving no history of scarlet fever	31	19	12	61

that there was a larger percentage of positive reactions in those who had never had scarlet fever than in those who gave a past history of the disease. It may be that in the individuals of the latter group, although originally hypersensitive, the cutaneous reaction of hypersensitiveness disappeared for variable periods of time in the process of desensitization from scarlet fever, to return in some and not in others

In view of the uniformly negative reactions in the 35 active cases of scarlet fever tested, it is conceivable that in such individuals the cutaneous sensitiveness to streptococcus protein has been destroyed, at least temporarily, by the reaction; such a reaction showing itself in the form of the characteristic signs and symptoms of scarlet fever. If this is so it is additional evidence to warrant the hypothesis that scarlet fever is nothing more than a reaction of hypersensitiveness to streptococcus protein. It must, of course, be kept in mind that such negative reactions may be non-specific in nature.

The question arises naturally, Is this positive reaction to streptococcus, found in our control experiments among fairly normal persons, one of hypersensitiveness, or is it a toxic, inflammatory effect analogous to the true positive Schick reaction in diphtheria? The evidence would seem to indicate that it is a reaction of hypersensitiveness to streptococcus protein. For example, if it were a toxic reaction, due to streptococcus, then, as is the case in a negative Schick test (where it is known that a negative test is evidence of immunity against diphtheria because natural antitoxin in the person's blood has neutralized the injected toxin, thus preventing its inflammatory action), so in a case of active scarlet fever with a negative test to streptococcus protein (as found in all cases of our study), it must be assumed if the test is toxic in nature that such a negative test is an indication of natural immunity or resistance to the toxic action of streptococcus. This argument, however, is not tenable. Considering the very definite etiological relation of streptococci to various complicating lesions of scarlet fever, it hardly can be argued that a person with scarlet fever has a specific immunity or resistance against the toxic products of streptococci.

Other factors which possibly indicate the anaphylactic or hypersensitive nature of the above described cutaneous reactions are their appearance and time of development. The positive Schick reaction (which is not "anaphylactic" in nature, but which is a typical example of a reaction of tissue to a toxic injury) appears as a trace of redness at the site of injection in twelve to twenty-four hours, becomes larger and more distinct in twenty-four to forty-eight hours, and reaches its point of maximum intensity on the third or fourth day, when it shows a rather circumscribed area of redness with some infiltration. It persists from five to

fourteen days and then fades, leaving a brownish, scaling area which may be evident for several weeks

The cutaneous reaction in our experiments, unlike the true Schick reaction, when positive has much the appearance and time of onset of the "pseudo-Schick" reaction (which is considered by most authorities to be a "hypersensitive" reaction). It usually appears early, four to eighteen hours; reaches its height in twenty-four to forty-eight hours; fades rather rapidly in three to four days, leaving little or no discoloration or scaling. At its height it is raised and dark red at the center, graduating off into a more or less secondary areola which is not definitely circumscribed, but has an irregular outline.

While the writer does not wish to imply that these experiments (limited as they are in number) are in themselves conclusive, it would seem that the results (considered in conjunction with the facts previously noted as to (1) the similarity of the signs and symptoms of scarlet fever to those of such manifestly "hypersensitive" states as drug and serum allergy, and (2) the admitted association of streptococci with scarlet fever) lend support to the thesis that scarlet fever is a generalized reaction of hypersensitiveness to streptococcus protein.

V. Discussion. A. EPIDEMIOLOGICAL OBSERVATIONS. From the standpoint of our hypothesis it is obvious that two persons may react differently to virulent human streptococci implanted in the throat or tonsils. One may develop a simple inflammatory reaction to the streptococcus infection resulting in a mild angina or a typical septic sore throat; but with no further marked constitutional signs to indicate hypersensitiveness to streptococcus protein (such a person being non-sensitive to this particular protein). The other individual may show not only a mild or severe sore throat as a result of the inflammatory reaction, but (being hypersensitive to the protein molecules of streptococcus, liberated through autolysis) also may show a scarlatiniform rash and other "hypersensitive" signs and symptoms typical of scarlet fever. Thus, scarlet fever might be described as a *compound* condition, made up of a streptococcus infection (either faucial or extrafaucial) plus an intoxication in a person who is hypersensitive to streptococcus protein. Many years ago Jenner[26] asked the question in regard to such diseases as scarlet fever: "May we not conceive than many contagious diseases now prevalent among us may owe their present appearance not to a simple but to a *compound* origin?" On this basis, it is suggested that the beginning, local symptoms of scarlet fever, such as angina, are due to an original streptococcus infection, while all other constitutional signs and symptoms of the disease are due to the autolysis of streptococci and the absorption of streptococcus protein, giving rise to a specific reaction of hypersensitiveness in those who are susceptible.

Such an interpretation of scarlet fever would explain not only the demonstrated relation of streptococci to the disease, but also would make clear the many cases of the disease apparently arising *de novo*—those unassociated with or unexposed to other typical cases. Such instances of scarlet fever may be considered to arise in hypersensitive persons who have been infected with streptococci from various virulent streptococcal lesions or from streptococcus "carriers." Scarlet fever following contact with objects associated in time past with cases of the disease may be due to the transfer of streptococci to hypersensitive individuals, giving rise to streptococcal protein intoxication. Scarlet fever appearing in individuals, such as physicians and nurses, who previously have been apparently "immune" to the disease may be explained on the ground that such persons heretofore not "sensitive" have become "sensitized" to streptococcus protein.

The varying severity of scarlet fever, in the light of such a theory, may be due to various grades of hypersensitiveness to, and the "dosage" of, streptococcus protein. It has been demonstrated by various investigators that anaphylactic or hypersensitive conditions depend largely on quantitatve factors. In other words, the larger the amount of foreign protein absorbed the greater the reaction in those who are hypersensitive. In this connection it is of interest to note the fact that, as a rule, the severity of scarlet fever apparently varies with the number of streptococci found in the throat. Malignant cases are usually associated with enormous numbers of virulent hemolytic streptococci, while mild cases are associated with comparatively small numbers. It must be kept in mind, also, that such living streptococci constitute a constantly reproducing source of protein poison. The further observation that not all persons intimately exposed to the disease contract it (not over 40 per cent according to some authorities) may be an indication that the majority of persons, except in the earlier years of life, are not hypersensitive to this particular bacterial protein, and when attacked by streptococcus they suffer only from the local inflammatory reactions, resulting in such symptoms as angina.

Smillie[4] cites an instance in which three little girls came together for a party. They were neither from the same home, nor schoolroom, and not exposed to any condition in common. At the time there was no scarlet fever in the neighborhood. Three days after the party all three developed sore throat. Two days after this one child showed a typical scarlet fever; the second had, in addition to a sore throat, a mild and questionable rash; the third child showed typical signs and symptoms of septic sore throat, but with no rash or other evidence to warrant a diagnosis of scarlet fever. From the throat cultures of all three children the hemolytic streptococcus was isolated and the three strains were exactly

alike culturally, serologically and in animal inoculations. Based on this, Smillie asks the following questions: "Were the first two children infected with something in addition to the beta-hemolytic streptococcus that produced scarlet fever in them? Is it possible that scarlet fever is due to two factors? Or did the third child really have scarlet fever without the rash?" From out standpoint the first two children were not "infected with something in addition" to the streptococcus. All three were infected with the same kind of organism, namely, the streptococcus; but two out of the three were hypersensitive (one more than the other) to streptococcus protein, while the third was not. It is not only possible, it is quite probable that scarlet fever *is* due to two factors: (1) Streptococcus infection, and (2) streptococcus protein intoxication. The latter will show itself only in those hypersensitive to this protein. This might explain the above described conditions of the three children.

In studies of an epidemic of scarlet fever at the Agricultural School of the University of Minnesota, in 1921, Diehl and Shepard[27] found that only 1 out of 66 intimately exposed persons developed the disease and that in only 15 out of a total of 59 cases of scarlet fever could definite proof of exposure to known cases be obtained. The control of this epidemic was brought about only when all persons showing "red throats" or angina were carefully isolated.

All of the above facts indicate that healthy and convalescent "carriers" of streptococci, as well as mild and missed cases of streptococcus disease may be of prime importance in the spread of scarlet fever to hypersensitive persons. Chapin[28] believes that the failure to properly control and prevent scarlet fever is due to the difficulty in locating and controlling "carriers" and missed cases. Chesley[29] emphasizes the fact that even "immunes" may be "carriers" of scarlet fever. The entire "carrier" problem, as it relates to the spread of scarlet fever, will be much simplified if our attention may be focussed on the streptococcus, and the actual prevention and control of the disease will be easier of accomplishment if we may look upon all human virulent streptococcal infections and diseases as potential sources of streptococcal protein intoxication, or so-called scarlet fever, in those who are susceptible. Based on our theory it may be said, that in isolating cases of scarlet fever to prevent the spread of the disease we have been shutting up only those poor unfortunates who are hypersensitive to streptococcus protein. What we, as physicians and health officials, should aim at is the proper isolation and treatment of *all* those individuals (personally fortunate in not being hypersensitive to streptococcus protein, but more dangerous to the public health and welfare), who have simple streptococcus infection or disease, or who are "carriers" of virulent streptococci.

In this same connection, Mironesco[30] is of the opinion that

scarlet fever may be spread by cases which show no sign of the disease except a sore throat. Shepard[31] also offers evidence to show that during an epidemic of scarlet fever which was carefully studied persons having only a mild angina apparently were the sources of typical scarlet fever in others. Laird[32] records a case of a hospital ward maid who recently had a sore throat, in fact, who had chronic enlargement of the tonsils and a deflected nasal septum, and who had from childhood suffered from sore throat. While her brothers and sisters had scarlet fever twelve years ago, she never showed symptoms of this disease. It was conclusively demonstrated that this ward maid—a so-called "healthy carrier"—had been the source of a recent epidemic of scarlet fever. Maclean[33] traced a milk-borne outbreak of scarlet fever to a milker who had a streptococcus sore throat but no evidence of true scarlet fever either before or after. On this milk route, in addition to the cases of scarlet fever, 29 cases of sore throat were discovered. These throats presented an identical appearance with those accompanied by a rash, but with milder constitutional symptoms. Johannessen[34] describes an instance in which a servant girl, while nursing a scarlet-fever patient, developed a mild simple tonsillitis. Three days later she returned to her home many miles away, situated in an isolated forest country. She was not ill enough to go to bed and showed no special signs of scarlet fever. She was out daily among her relatives and friends. Scarlet fever immediately became epidemic, 24 families and 67 persons out of a population of 533 persons being affected. No imported case of typical scarlet fever to cause such an epidemic was found. Each of the above described persons, although individually not hypersensitive to streptococcus protein, and hence not having scarlet fever, may have carried the streptococcus or may have been the source of streptococci carried to different groups of persons containing a certain proportion of hypersensitive individuals.

The apparently contradictory evidence as to the possibility of experimentally or artificially transferring scarlet fever from one person to another, recently summarized by Hektoen,[45] from the viewpoint of our theory might be explained by assuming that such results naturally would be expected to vary and even to be contradictory, depending upon the presence or absence of hypersensitiveness to streptococcus protein in persons involved in the experimental inoculations. Moreover, if streptococci remain localized in the throat or some other site, such as the uterus, and there give off their protein poison, it probably would not be possible to transmit the disease by inoculation with blood or other body fluids which might be sterile.

B. Practical Applications. If scarlet fever is a manifestation of streptococcus protein hypersensitiveness it is evident that the prevention as well as the treatment must be aimed at (1) the

streptococcus in general, and (2) the hypersensitive state of the individual.

In the prevention of scarlet fever the necessity for isolation of *all* frank cases of the disease, as well as various other virulent streptococcus infections or diseases, has been emphasized. It is hardly necessary to suggest also that adequate, concurrent and terminal disinfection of all fomites and discharges in such diseases are of equal importance. In addition to this, the use of anti-streptococcus vaccines or sera may be logical in combating the streptococcus *per se*. However, the use of vaccines by the usual methods of dosage may be of no value in the actual control or treatment of scarlet fever for the reason that instead of combating the disease in certain susceptible persons, the disease, or hypersensitive attack, may be actually initiated or intensified. This may explain the rather contradictory results in the use of streptococcus vaccines and antisera. Better results possibly may be obtained by giving streptococcus vaccine from the standpoint of inducing a specific desensitization, that is, by very small initial doses gradually increased.

Even though living virulent streptococci may be present in the throat and tonsils, much may be done to prevent or at least to decrease the multiplication of these organisms and the absorption of streptococcus protein into the lymph and blood. Thus Milne's prophylactic, which involves the swabbing of the tonsils and pharynx with a 10 per cent solution of phenol in oil, may be of distinct value in decreasing the multiplication and autolysis of streptococci and the consequent absorption of streptococcus protein. Like results may be obtained by the use of a 1:2000 mercury perchloride throat spray as recommended by Thornton,[35] or a spray of pyocyanase as suggested by Sauer,[47] or an insufflation of sodium sozoiodolicum with sulphur as used by Rubens.[48] Moreover, the anatomy and pathology of the tonsils may be important in determining the reaction of the body to streptococcus protein. Bullowa[36] believes that the mechanical pressure action of swollen tonsils or the squeezing of large tonsils in the act of swallowing readily permits or aggravates the passage and absorption of the scarlet fever "virus" into the system. If this is true, judicious tonsillectomy may be of great value in the prophylaxis against scarlet fever. Furthermore, Bullowa recommends in the treatment of scarlet fever involving very large, inflamed tonsils that the crypts be drained and if necessary that the plica be incised to relieve pressure effects. This would be a logical treatment in the light of our theory and findings. Tonsillectomy during the course of scarlet fever probably is not always a wise procedure, as the raw, bleeding operation wound may be a means of more ready absorption of "virus," or protein, into the lymph and blood stream. In fact, cases have been seen in which much aggravation

of all scarlet fever symptoms has followed tonsillectomy during the course of the disease.

In a consideration of the possibilities for bringing about a desensitization of the person to streptococcus protein in both the prevention and treatment of scarlet fever from the standpoint of our theory, we must inquire briefly into the phenomenon of so-called antianaphylaxis. By various observers it has been found that following anaphylactic shock a refractory state is evident, that is, the animal which was previously sensitive no longer reacts in like manner to subsequent injections of the same antigen. This phenomenon, while not always permanent, is analogous in some ways to that of immunity against bacterial infection. Antianaphylaxis may be acquired either by having an anaphylactic attack or it may be induced artificially. Such induced antianaphylaxis may be divided into (1) non-specific antianaphylaxis, and (2) specific antianaphylaxis. Non-specific antianaphylaxis may be brought about by the ingestion or injection of certain drugs, foreign sera, peptone or other proteid substances. The chief drugs which have been reported to have preventive or curative influence are atropine sulphate, adrenalin, chloral hydrate and lecithin, the first two giving the most uniform results. The beneficial effects in the treatment of scarlet fever by the use of convalescent or normal whole blood or serum may be based at least partially on the production of a non-specific antianaphylaxis. The very fact that normal blood is reported by Moog[49] to have nearly as much therapeutic effect as blood from convalescents is an argument in favor of the non-specific nature of the protective reaction induced. Specific antianaphylaxis, according to Coca,[2] may be induced: (*a*) By desensitization with small, slowly injected doses at proper intervals of the specific antigen; (*b*) by antibody protection, through the re-injection of the specific antigen just before the suspected development of the hypersensitive state. Such specific desensitization is not so evident in serum allergy and other forms of allergic hypersensitiveness as in experimentally produced anaphylaxis and often is difficult to accomplish. Until some accurate method for such specific desensitization to streptococcus protein can be developed, it may be wise to depend on various methods of non-specific desensitization in the control and treatment of scarlet fever.

Auer[37] demonstrated that 3 mg. of atropine sulphate injected subcutaneously in guinea-pigs would save the animals from acute anaphylactic shock and death. This drug has been used with good effect in some cases of scarlet fever, and is said to lessen the susceptibility to the disease. Adrenalin is another drug which by some is considered almost a specific in the prevention or treatment of experimental anaphylactic shock. It is interesting to note that various authorities have advocated the use of adrenalin in the treatment of scarlet fever, especially in severe malignant cases

with marked depression or "shock." Thus, Hutinel[38] recommends the slow, intramuscular injection of a small amount of a 1:1000 solution of adrenalin in saline. In cases of scarlet fever with sudden collapse, Meara[39] suggests the use of adrenalin by the skin in a dose of 10 drops of a 1:1000 solution, slightly less by the muscle, and 2 to 3 drops by the vein in adults. For a child of five years he uses one-quarter the above doses, and for a child of ten to twelve years one-half the above doses. Meara believes the action is most certain when the drug is given by the vein. He wisely cautions against the careless use of adrenalin on account of its rapid action on the blood-pressure and heart. Rolleston,[40] as well as Kramer,[41] also have noted good results in the treatment of scarlet fever by the judicious use of adrenalin.

One of the chief non-specific antianaphylactogens is peptone. In 0.4 to 0.5-gm. doses by mouth this protein may act as a desensitizing agent and apparently is polyvalent for most of the proteins causing hypersensitiveness. Peptone may be given by mouth or be injected subcutaneously or intramuscularly. In an account of peptone therapy, Fatou[42] indicates that he has obtained excellent results in the treatment of various hypersensitive conditions by the administration of 0.5 gm. of peptone one hour before each meal by mouth. This may be administered three times a day for a week then suspended for a week, or it may be given rather continuously. It is necessary that peptone for therapeutic purposes shall be of good quality. As Auld[43] has shown, if peptone contains histamine very severe and troublesome reactions may occur. The administration of pure peptone by mouth gives rise to little or no reaction, while in some instances it has resulted in very severe reactions when given subcutaneously, intramuscularly or intravenously. Even such intense reactions often have been followed by excellent therapeutic results.

With the above facts in mind, it would be of interest from the viewpoint of our theory to test the results of peptone therapy in scarlet fever; also to test its possible prophylactic power in protecting contacts from attacks of the disease. If positive results should be obtained it would lend therapeutic confirmation to our hypothesis, and be an important step in the prevention and treatment of scarlet fever. This will form the basis of a future communication.

VI. Summary. 1. Based on original observations made during the last fifteen years, an attempt is made in the first part of the present study to demonstrate the almost complete uniformity in the clinical signs and symptoms of drug allergy, serum allergy and scarlet fever.

2. Based largely on the investigations of other observers, it is emphasized in this study that virulent hemolytic streptococci are

present, frequently in pure culture, in practically 100 per cent of scarlet fever throats, and that they are neither so generally present, nor in such enormous numbers in other diseases or normal throats; moreover, streptococci frequently have been found in the blood and complicating lesions of scarlet fever, and for many years have been suspected of having an etiological relation to this disease.

3. By the use of cutaneous protein sensitization tests it is demonstrated in the experimental part of this study that various apparently normal individuals who have had scarlet fever in the past or who never have had the disease show from 41 to 61 per cent of positive reactions when tested with streptococcus protein. On the other hand, cutaneous tests with streptococcus protein on individuals during the active course of scarlet fever, particularly in the early stages, are found to be uniformly negative. From this it may be concluded that while a fair proportion of normal persons are hypersensitive to this particular bacterial protein, individuals with active cases of scarlet fever apparently are in a state of desensitization.

4. It is suggested, therefore: (*a*) That scarlet fever is a reaction of specific hypersensitiveness to streptococcus protein; (*b*) that scarlet fever is a compound condition, involving primarily a local streptococcic infection (usually of the throat, but frequently of an accidental or operative wound, burns or associated with the puerperium); and secondarily, a streptococcus protein intoxication in those who are hypersensitive.

5. On the basis of such a theory, it seems probable that the prevention and treatment of scarlet fever also may depend on two factors: (*a*) The control of the streptococcus *per se* through adequate isolation and concurrent and terminal disinfection of all cases, including not only frank scarlet fever but also all other virulent streptococcus diseases; as well as the isolation and treatment of all streptococcus "carriers," and proper attention to milk and other possible vehicles of streptococcic infection. (*b*) The desensitization of individuals who by cutaneous tests are shown to be hypersensitive to streptococcus protein, either by specific (vaccines or antisera) or non-specific (protein or serum) methods of treatment; and adequate attention to local sites of streptococcic infection, such as the throat, to reduce to a minimum the possible absorption of streptococcus protein.*

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MODERN METHODS OF TREATING LOBAR PNEUMONIA.*

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To confine one's entire attention to the newer methods of treating lobar pneumonia would be to neglect the still most important aspects of the therapy of the disease. It is only necessary to look back over the almost countless list of discarded therapeutic measures to convince ourselves of the wisdom of the remark made by Juergensen, "Nature cures, and the only duty of the physician is to maintain life until this cure is effected."

Of late years the increase in knowledge of the etiological agents responsible for lobar pneumonia has led to an increased activity among therapeutists to develop specific forms of treatment. Specific sera, vaccines and chemicals all have their advocates and it is to these measures that we shall return after a brief consideration of the most important general methods.

General Regimen in the Care of Pneumonia. The toxemia of lobar pneumonia is of a sharp, sudden, severe type seen in few other diseases. Lasting, as it ordinarily does, only about seven days, the necessity of building up the body tissues is not an important one. We must do nothing to interfere with elimination (by stopping up the bowels); otherwise we may feed as we like. On the other hand it is essential to increase every form of elimination possible and to this end fluid forced to 3 to 4000 cc daily, allows the kidneys, bowels and skin to function best in this respect. Should vomiting or delirium interfere with the fluid intake subcutaneous injections of salt solution or Murphy drips may be resorted to.

The severity of the toxemia is frequently revealed by a failing myocardium. We must spare no effort to relieve the heart muscle from the very onset of the disease. Of great importance in this respect, is the prevention of any movement on the part of the patient. This, in my opinion, is the most valuable contribution that can be made by the trained nurse. The patient must be lifted whenever he even so much as turns in bed. I know of four patients who have died while, or immediately after, using a bedpan. The physician should make this clear not only to the nurse but also to the patient, care being used, of course, not to alarm the latter unnecessarily. All forms of treatment which require exertion on the part of the patient must, therefore, be modified. Recent studies by Levy have shown that the digitalized heart does not dilate as readily during pneumonia as the undigitalized controls. This would seem to be sound argument for the early administration

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of digitalis. Certain it is, however, that digitalis in some form is urgently indicated at the first sign of myocardial insufficiency. The powdered leaves may be used by mouth but a more rapid and certain method of administration is digitalin or digifoline hypodermically. Sudden heart failure may require, in addition, the use of morphine and atropine or even venesection. Caffein (sodio-benzoate) and camphor (in oil) are stimulants to be used when necessary after the full amount of digitalis has been given or when additional stimulation is required.

The toxemia may also make itself felt on the peripheral circulation in the form of vasomotor paralysis and this is best combated, or rather best prevented, by hydrotherapy in the form of cold sponging every three or four hours. As cautioned before it is ill advised to move the patient and so the sponging may be confined to the anterior surface of the body and the extremities. Moving the patient into a tub is absolutely contraindicated. Epinephrin or pituitrin are sometimes helpful in raising the blood-pressure by action on the peripheral vessels and strychnine may act by stimulating the medullary center.

Perhaps the commonest result of the severe toxemia is abdominal distention due to paralysis of the intestinal musculature. Few cases run the course of lobar pneumonia without at some time being disturbed by tympanitis and it should be anticipated and treatment instituted at the earliest moment. Turpentine stupes are often sufficient to relieve slight degrees of distention (hot turpentine stupes to be applied for twenty minutes and then replaced by hot-water stupes for twenty minutes and then the process repeated) especially if a rectal tube be inserted. More marked or persistent distention may require turpentine enemata (turpentine, 15 cc to 1000 cc of water) or glycerin enemata (glycerin, 120 cc followed by water 60 cc injected high in the bowel), and if these fail pituitrin 1 cc hypodermically, repeated in a half hour, may prove efficacious. Elimination of milk from the diet may be necessary as well. When the patient is first seen he should be given a cathartic if none has already been taken and this should be followed the next morning by a saline purgative. After this enemata may be relied on to cleanse the bowel every second day inasmuch as the diet contains very little residue.

Pain is one of the very troublesome symptoms in some cases. It is produced by the pleurisy which accompanies the pneumonitis and is the cause for the rapid and shallow breathing so often seen in the early stages of the disease. Morphine is often required to quiet this pain but it is advisable to use as small a dose as possible on account of the paralyzing action which morphine exerts on the intestinal wall. Enough relief may be gained from $\frac{1}{16}$ or $\frac{1}{12}$ of a grain to enable the patient to fall off to sleep and this dose may with absolute safety be repeated often. Before

morphine is resorted to an ice-bag should be tried and if this is found unavailing a tight chest swathe applied. The non-productive coughing should be stopped by heroin (easily given in lozenges containing heroin, gr. $\frac{1}{12}$).

Delirium must be controlled and if morphine alone fails Schlesinger's solution may exert a quieting effect. Occasionally its effect is just the opposite and it serves only to increase the restlessness.

If cyanosis and dyspnea become prominent symptoms great relief may sometimes be had from the administration of oxygen. This is best done in a suitable oxygen chamber but quite satisfactory results can be obtained by bulbing the oxygen through a water jar and into a soft-rubber catheter which has been introduced through the nose to a point where its tip is just visible back of the soft palate. This method is less disturbing to the patient than the funnel and is also more easily performed by the attendant. Fresh, cool air is most comforting to the patient and aids in reducing any restlessness. Exposure should be avoided.

Doctor's Orders. Absolute rest (give details).

Force fluids to 3000 cc.

Soapsuds enema every two days if necessary.

Cold sponging if necessary for temperature over 103° F. every three hours without moving patient.

Ice-bag to head or chest for pain.

Chest swathe for pain when needed.

Morphine, gr. $\frac{1}{12}$ (hypodermically) for pain if necessary; repeat in one hour if necessary.

Turpentine stupes if necessary for distention.

Digitan, gr. $1\frac{1}{2}$, every four hours for 12 doses.

Specific Therapy.

SERUM.	Horse (Cole *et al.*)
	Antibody extract(Huntoon).
	Chicken (Kyes).
	Convalescent human serum (Stengel).
VACCINE.	Prophylactic (Austin and Cecil).
	Therapeutic (Rosenow).
CHEMICAL.	Quinine.
	Numoquin (Optochin).
	Alkaline.

Of the eight kinds of specific therapy charted above the Type I pneumococcus serum developed by the Rockefeller Institute workers is the only one that has received enough of a trial to warrant analytical discussion.

Kyes' chicken serum (prepared by further immunizing the already immune chicken to the various types of pneumococcus) has been used in Chicago in the Cook County Hospital and also

tried at Camp Grant. The statistics relative to the case mortality are suggestive (a reduction from 45.3 per cent to 20.8 per cent in the Cook County Hospital, and a mortality of 7.7 per cent in 322 treated cases at Camp Grant) but the reactions following its use coupled with other reasons led to modifications and I have seen no further statistics.

An attempt to use therapeutically the immune serum obtained from convalescent pneumonia patients by bleeding them soon after their crisis was made in Philadelphia by Dr. Stengel and reported last year. This method is not only attended by great technical difficulties but is also open to many theoretical objections. The chief objection is that serum from convalescent patients is never found to be as rich in specific antibodies as is the serum produced by animal immunization, and treatment with this latter form of serum has already been discarded as useless in all types except Type I. (I allude of course to serum from animals immunized to Types II, III and IV pneumococcus.)

Prophylactic vaccination with killed cultures of Type I, II, III, pneumococcus was performed by Austin and Cecil on 12,519 soldiers at Camp Upton. During a comparatively short period of observation the control group showed many more pneumonia cases, and, more upper respiratory infections as well, than did the vaccinated group, and it was noted that what cases did occur were of a very much milder form. We can hardly all of us be vaccinated every November but in suitable cases this form of treatment may be of real service.

Rosenow developed a partially autolyzed vaccine with which he treated cases of pneumonia. Little is known as to the variety of cases treated but his mortality in a group of 200 cases was as low as 7 per cent. This method has not met with general acceptance and it has not been given a sufficient test so that we must pass it by with a mere mention.

Of the drugs which from time to time have been advocated quinine has recently returned to prominence as a specific in pneumonia. Many years ago it was used very frequently as an antipyretic and therefore often in pneumonia. In 1911, Morgenroth and Levy announced the discovery of a quinine salt which they called optochin. In the test tube this drug was found to have an almost unbelievable power to kill the pneumococcus. No very extensive therapeutic tests were made in this country as it was soon learned that occasional toxic manifestations were accompanied by lesions in the optic nerve. In Germany, however, a basic salt has recently been prepared which is said to be harmless and at the same time very efficacious in the treatment of lobar pneumonia. This substance is known as numoquin. It is brought to your attention now because the writer believes that when sufficient knowledge about its use is obtained we shall have a most valuable adjunct to

our armamentarium. Until that time however we may, if desired, safely turn to quinine which is said by some writers (Cohn-Bronner) to surpass optochin. Painful local reactions usually follow the hypodermic injection of quinine so that a high dilution is necessary. One satisfactory preparation which may be obtained at any drug store is:

℞—Quinine muriate 2.0
Urethane 1.0
Aqua dist. . . . . q. s. ad 20.0
Sig.—5 cc intramuscularly—repeat in twenty-four hours and again forty-eight hours later if necessary.

Alkaline treatment has been advocated by many clinicians but the most thorough study of this phase of the condition (made by Means) has demonstrated that not every case suffers from an acidosis. Means points out that the production of an alkalosis not only may readily occur but also is quite dangerous. To avoid this it is necessary to make frequent observations on the alveolar air and the blood CO_2. This fact complicates the procedure to such an extent as to make it inapplicable for general routine use.

The form of specific therapy with which the writer has had most experience is Type I antipneumococcus serum. During the War he was stationed for three months at the Rockefeller Institute Hospital and from there sent to Camp Meade to treat the pneumonia cases. The first winter there (1917 to 1918) the writer personally treated 50 cases of Type I pneumonia with serum obtained from Mulford.

TABLE I.—TYPE I, LOBAR PNEUMONIA (CAMP MEADE)

	Number.	Died.	Mortality, per cent
Treated	50	3	6.
Untreated	7	0	0.
Total	57	3	5.3

It will be noted from Table I that only 3 cases died and it should be added that 1 of these 3 was treated first on the sixth day of the illness having been brought in moribund; 1 had a tuberculous cavity which practically involved the whole left upper lobe, and the third, though operated on by mistake for a suspected empyema before being seen by our service, was apparently cured of the pneumonia only to die ten days later from a meningitis. In the treated group there were no complications other than those mentioned above. There was unfortunately no control group.

Two years later while resident at the Boston City Hospital, the writer supervised the treatment of 75 cases of Type I pneumonia with serum obtained from the Massachusetts Board of Health. The cases comprised men and women of all ages and varieties of physical condition, admitted, many of them, late in the disease. The

mortality rate in this group of cases was 17.3 per cent. Of these cases (56 cases) which were treated during the first week of the disease only 7 died, giving a mortality of 12.5 per cent.

During the next two years, under Dr. E. A. Locke's direction, every serum treated case was controlled by a similar untreated case. The controls were made to compare clinically as nearly as possible to the treated group. It will be seen from the Table (II) that the mortality in each group was about 17 per cent.

TABLE II.—MORTALITY, RATE, 145 TREATED: 71 CONTROL CASES (BOSTON CITY HOSPITAL).

	Number cases.	Number deaths.	Mortality, per cent.
Group A	75	13	17.3
Group B	70	12	17.1
Totals	145	25	17.2
Control Group B	71	12	16.9

In a recent address delivered before the New York Academy of Medicine, Dr. Locke carefully analyzed the serum treatment of pneumonia and brought out, among many interesting points, the fact that the average mortality obtained in 6 civilian hospitals in Boston, New York and Baltimore was 19.3 per cent. From 11 Base Hospitals in the various army camps, however, an average mortality of 9.5 per cent was obtained, and the Rockefeller Institute Hospital figures show 195 cases treated with a mortality of 9.2 per cent. These statistics seem to show that, although serum treatment of Type I lobar pneumonia is of definite value in reducing the case mortality, it is a procedure which requires exceptional facilities and the service of highly trained specialists.

Cecil at the Bellevue Hospital, and Connor at the New York Hospital, have for the past few years given a thorough trial to a new form of treatment. This consists of the administration of a polyvalent antibody extract prepared by Huntoon of the Mulford Laboratories from horse serum which has been highly immunized against the fixed types of pneumococcus (Types I, II and III). This preparation is a protein-free suspension of specific antibodies in salt solution. The results from treatment with this preparation obtained at the Bellevue Hospital are summarized in Table III.

Dr. Cecil, who has very kindly loaned the writer some of his lantern slides, asks that it be made clear that the intravenous injection of this substance late in the disease is attended by many severe reactions which, in a few instances, have terminated fatally. For this reason subcutaneous injection of larger amounts is now being tried and the results will soon be announced. Both Dr. Cecil and Dr. Connor feel encouraged to go on with this work on account of the very definite indication of the value of the method. If circum-

stances are favorable this preparation will soon be available for general use.

TABLE III.—COMPARISON OF DEATH-RATE IN TREATED AND CONTROL SERIES

Antibody Wards:				Control Wards:			
Type.	Cases.	Deaths.	Rate, per cent.	Type.	Cases.	Deaths.	Rate, per cent.
Pn. I	158	21	13.3	Pn. I	162	36	22.2
Pn. II	83	23	27.7	Pn. II	67	27	40.3
Pn. III	73	29	39.7	Pn. III	60	24	40.0
Pn. IV	110	18	16.4	Pn. IV	121	29	24.0
Total	424	91	21.4	Total	410	116	28.3
Strept., etc.	48	24	50.0	Strept. etc.	35	12	34.3
Unclass.	36	14	38.8	Unclass.	47	20	42.5
Gr. tot.	508	129	25.3	Gr. tot.	492	148	30.0

Summary. 1. We must never lose sight of the importance of general therapeutic measures in the treatment of lobar pneumonia.

2. Of the special measures Type I antipneumococcus serum is the only one which has given satisfactory results in a large enough series to warrant its further use.

3. Quinine therapy seems very promising and may subsequently prove to be of great value.

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THE IMPORTANCE OF ATAVISM IN THE DIAGNOSIS OF HEREDITARY HEMORRHAGIC TELANGIECTASIA.

RATIONALE OF TREATMENT AND REPORT OF AN ADDITIONAL FAMILY.

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Clinical interest in hereditary hemorrhagic telangiectasia dates from the paper of Sir William Osler,[4] in 1901. Rendu,[3] however, in 1896, was first to associate familial epistaxis with the multiple telangiectases that together constitute the chief features of this pathological entity. It may be defined as an hereditary abnormality characterized by the formation of localized dilatations of capillaries and venules which occur chiefly in the skin of the face and in the mucosa of the nose and mouth and which may give rise to apparently spontaneous hemorrhages, most commonly in the form of recurrent epistaxis.

Among 30 families affected with this disease which are reported in the literature, there are found 57 undoubted and fully detailed cases and 155 other probable cases which are only incidentally mentioned. In addition to these 212 cases occurring in 30 clearly affected families there have been reported a number of isolated, apparently non-hereditary cases which conform so closely to the disease under consideration that one is forced to class them in the same group. For purposes of analysis in this article, however, only the 57 fully reported cases are utilized. A chronologically arranged bibliography is appended.

Analysis of the reports in the literature seems to justify the conclusion that atavism has been overlooked as a factor in the heredity of this disease. Furthermore there are certain misconceptions regarding the mechanism of the hemorrhages. The purpose of the present article is to discuss these two factors and to point out their importance respectively in the diagnosis and treatment of the disease.

The appended detailed case report may serve in lieu of formal review of this somewhat unusual condition.

Atavism. It is commonly believed that there are no "skipped generations" in the inheritance of this disease. The best review of the subject is that of Steiner.[21] His diagrams show clearly that there are instances of atavism among the families reported by him as well as among those of older authors reviewed in his paper. But he makes no mention of this factor and has apparently missed its significance. Goldstein,[24] in a recent extensive review, epitomizes a

number of the isolated, apparently non-hereditary cases previously alluded to. He also fails to recognize the factor of atavism in the classical cases and accordingly fails to realize that most of his "non-hereditary" cases should properly be regarded as atavistic instances of hereditary telangiectasia. A review of most of the recent text-books and systems of medicine shows that this factor is not generally recognized—the only mention at all concerning it being that of Stevens,* who states that the disease "shows little atavistic tendency."

I find seven clear instances of atavism in four of the thirty families reported as exhibiting the disease in classical form:

Osler's[4] first patient, "George B," had a grandniece, granddaughter of "the patient's elder sister who was herself afflicted with the disease." This grandniece "had frequent epistaxis." "None of his (George B.'s) nephews or nieces have bled." Therefore, from a clinical standpoint at least, the mother of this "grandniece" was free of the disease yet transmitted it to her daughter.

Steiner's[21] first two families show most interesting examples of atavism. In his first family there are two instances of atavistic transmission (one by female and the other by male, neither of whom showed signs of the disease) to their respective offspring. His second family comprised patients in the second and third generations of a family whose "first generation" showed no evidence of the disease. Moreover the afflicted individual in the third generation came of a non-affected parent of the second generation, so that this case harks back to some ancestor at least two generations removed.

Audry's[22] family of four affected generations "started" from apparently non-affected grandparents although on one side of this non-affected pair were two affected members in the same generation.

Weber's[8] family showed a patient in the fourth generation whose taint was transmitted through the father (himself free of symptoms) from an afflicted grandmother in the second generation.

Of course it may be that the non-affected "carriers" of this hereditary abnormality are merely clinically free of symptoms and on careful examination might show some of the minute vascular defects that characterize the disease. But this is beside the point. Practically speaking we have to admit 7 clear cases of atavistic inheritance among 212 cases mentioned in the literature. Moreover, one of these skipped two and possibly more generations. It would not be surprising then that many other like sufferers might well be unaware of the occurrence of nose-bleeding or telangiectases in their ancestors. A situation analogous to this occurred in one of Osler's cases which was at first not accepted as an authentic example of the disease because the patient knew of no afflicted relatives. "Later," as Steiner remarks, "another member of the family, similarly affected, was discovered."

* Practice of Medicine, Philadelphia, 1922, p. 718.

In the light of such cases as these we are forced to recognize a number of others reported in the literature under various names (but heretofore excluded from this pathological entity) as, most certainly, atavistic examples of hereditary hemorrhagic telangiectasia. A bibliography of such cases is also appended, although it is probably by no means complete.

Diagnosis. The presence of a typical family history makes the diagnosis easy in many instances. But a review of the errors in diagnosis that have been recorded shows that this does not always obtain. Seven cases were thought to be examples of hemophilia by the authors reporting them (Legg,[1] Rendu,[3] Chiari,[2] Coe[26]). This mistake would hardly be made at the present time, for the line of hereditary and sex incidence are entirely different and in hemophilia there is greatly prolonged coagulation time together with a tendency to bleed unduly from slight traumatism of normal tissue, both of which are absent in this disease. The patient reported by Hutchinson[19] had previously been treated for pernicious anemia. One of Steiner's[21] patients had had a small lesion excised from the tongue as a carcinoma which in all probability was simply a telangiectatic spot.

The author's patient had been previously diagnosed "chronic purpura hemorrhagica." This error would have been rendered unlikely by the proper evaluation of the family history and would have been avoided entirely by the simple test of pressing a glass slide against the purpuric-like lesions. Telangiectases of the sort found in this disease disappear under sufficient pressure while purpuric spots do not. The latter are fugacious while telangiectases are more permanent. There are only three instances recorded in which some of the telangiectases disappeared spontaneously. In purpura hemorrhagica the blood platelets are usually greatly reduced; they are apparently normal in hereditary hemorrhagic telangiectasia.

Finally, in all cases of obscure hemorrhage this disease must be borne in mind; and here it is that the role of atavism becomes one of major importance.

The absence of characteristic family history does not exclude the possibility of this disease.

Judging from Osler's[4] patient who came to autopsy and from the history of Richardson's[20] patient, gastro-enteric hemorrhages might well be the leading symptom in a given individual.

A brother of the author's patient died of "hemorrhages from the throat" which were said to be due to tuberculosis but which in all probability were from pharyngeal telangiectases.

Neurologists have reported a number of cases of cortical angiomata causing epileptic and hemiplegic symptoms. Goldstein's[24] patient had hemiplegia at forty years of age without any evidence of lues, hypertension, cardio-renal disease or arteriosclerosis. He attributes this to rupture of cortical telangiectases.

Several of the patients reported have had metrorrhagia and menorrhagia without any obvious cause, indicating the probability of telangiectases in the mucosa of the birth canal.

None of the classical cases has exhibited hematuria or other evidence of telangiectases in the urinary tract. Nevertheless it is interesting to speculate as to the possible relationship of this disease to certain cases of so-called "essential hematuria." Urologists have reported a number of such found at operation to be caused by small varices and angiomata of the renal pelvis. Particularly suggestive is the group of "hereditary hematuria" cases reported by Pearson,[39] Aitken[38] and others. The hereditary tendency recorded in these is identical with that of the disease under consideration, both sexes transmitting the disease and both being equally affected. No mention however, is made of telangiectatic lesions or of epistaxis in these individuals so that as far as the records go the analogy is incomplete.

Prognosis. The prognosis of this disease is sufficiently grave to demand our best therapeutic efforts. Although the outlook, *ad vitam*, is good, the prospects *ad valitudinem*, are decidedly poor. The majority of these patients at the time of their reports (average age forty-two) were semi-invalids. The hemorrhages tend to increase in frequency and severity as middle life is reached, and the nervous and physical strain of these repeated losses of blood make the plight of these unfortunate individuals very miserable indeed. A few however have not been incapacitated.

Of the 57 reported patients, only 1 died of the disease itself (Kelly's[6] patient, who died of epistaxis at the age of forty-eight years). Of the 155 additional patients mentioned, 5 died of epistaxis (average age forty-five years), 1 died of convulsions presumably from cerebral hemorrhage at the age of three years, and 1 died of "hemorrhages from the mouth" as did also the brother of the author's patient. Thus 8 of 812 (approximately 4 per cent) died of the disease itself. A "follow-up" of the others would probably show the majority dead long before their time, due to intercurrent maladies dependent upon their weakened condition.

Mechanism of the Hemorrhages. The hemorrhages constitute the only important therapeutic indication in this disease, except possibly the cosmetic features incident to the telangiectases themselves. The mechanism of these hemorrhages has been explained in two different ways: One hypothesis postulates some underlying hemorrhagic diathesis or blood dyscrasia as the determining factor. The other maintains that the telangiectases are primary and that the hemorrhages are mechanical by-products resulting from the rupture of these vascular defects.

Steiner,[21] it would seem, adheres to the "hemorrhagic diathesis" view although he does not use the phrase and seems to disregard his theory in consideration of treatment. He says "the bleeding

in these cases is often so severe that a condition of marked anemia is induced which may be an important factor in the development of the telangiectases. Certain it is that bleeding generally precedes the formation of these . . . and may do so with many years intervening." The inference from the above is that Steiner regards the hemorrhages as primary (due to hemorrhagic diathesis) and the telangiectases secondary thereto.

The author is convinced of the contrary. Bleeding does not precede the formation of telangiectases although bleeding may, and usually does, precede their discovery. All the evidence points to the probability of an early and prior age of formation of the intranasal lesions in patients exhibiting early epistaxis. Perhaps Steiner means simply that *additional* telangiectases are caused by the anemia.

The "chief complaint" in 40 of the 57 patients (70 per cent) is recurrent epistaxis since childhood. Telangiectases, however, are not discovered as a rule until adult life is reached. For, in the first place, these lesions do not appear on the face and other cutaneous surfaces until after twenty years of age in most instances. Why this is we do not know. In the second place, these patients, although exhibiting epistaxis since childhood, apparently do not consult physicians until adult life is reached when secondary constitutional symptoms drive them to seek help. The significant fact here, however, is that every one of the few juvenile subjects examined by rhinoscopy showed intranasal lesions. Furthermore in practically every reported patient exhibiting epistaxis who was subjected to rhinoscopy (44 of the 57) telangiectases were found. Judging from these facts we conclude that the formation of intranasal lesions is the earliest manifestation of the disease in all patients exhibiting initial epistaxis.

The mechanistic hypothesis of the hemorrhages is further strengthened by the following considerations: No patient suffering from this disease in classical form* has bled abnormally from trauma other than from traumatized telangiectases. None has had spontaneous bleeding of any sort other than from obvious or presumable telangiectases (excluding hemorrhoids). By "presumable telangiectases" are meant such instances as the following: the patient of Richardson's[20] that had melena and became sallow and weak before epistaxis appeared or spots were noted, caused (as the autopsy of Osler's patient would lead us to presume) by preformed telangiectases in the gastro-intestinal tract: or the author's patient who had metrorrhagia and menorrhagia at intervals from puberty until her first pregnancy due, presumably, to telangiectases in the birth canal which were wiped out during labor, as she had very little of this form of bleeding afterward.

* Legg's patient is an apparent exception, subject, however, to other explanation than that given in the report.

Blood studies by most authors have revealed no abnormality except secondary anemia. Blood coagulation time is normal in uncomplicated cases*—as shown in the reports of Osler,[4] Hutchinson and Oliver,[19] Goldstein,[24] Hanes,[13] Steiner,[21] Richardson[20] and the author. The blood platelets are normal (Steiner and the author).

On the basis of the foregoing facts we may conclude that the hemorrhages are the result of rupture of the thin-walled, superficial vascular defects that characterize the disease. This rupture may be brought about in a variety of ways—slight traumatism, insignificant irritations, vasomotor or mechanical congestion. It is suggestive that 8 patients are recorded as awaking frequently at night to find the pillow wet with blood from epistaxis. The intranasal congestion which probably occurs during sleep, doubtless determines telangiectatic rupture in such instances.

Treatment. The treatment of the disease has been very unsatisfactory, due, according to the author's opinion, in some instances to lack of faith in the purely mechanistic cause of the hemorrhages and in others to lack of zeal in pushing this conception to its ultimate therapeutic conclusion.

Only 2 therapeutic clinical cures are recorded, 1 by Hutchinson and Oliver[19] and 1 by Chiari[2] both of whom destroyed their patients' offending lesions by thermal cautery. Most modern authors recommend similar local treatment but none seems to have emphasized its all-important features.

My opinion is that a painstaking, methodical destruction of all bleeding telangiectases, by thermal or chemical cauterization, under local or general anesthesia, will result in clinical cure of most of these patients. Lesions of the skin, lips and tongue are most thoroughly and permanently destroyed by the electric needle (diathermy). The difficulty lies chiefly in the cure of epistaxis. Here the assistance of a patient, skilful rhinologist is of great importance. The exact location of intranasal lesions must first be determined. Then begins the task of thorough cauterization. For this purpose the best seems to be the chromic acid crystal, fused on the tip of a metal applicator and touched directly against the lesion to be destroyed. The same lesion may require several applications before it disappears entirely. Not more than two or three lesions should be cauterized at one sitting. Cocainization of the mucosa is sufficient anesthesia for this. In a difficult case where for anatomical reasons the offending spot cannot be reached, more radical measures must be employed, such as submucous resection of the nasal septum or removal of all or part of a turbinate body with a view either to remove thereby the bleeding lesion or to gain better access to it for cauterization. The danger of producing rhinitis sicca must be

* Freudenthal[25] has recently reported an apparent exception. His patient is said to have had a coagulation time of sixteen minutes which, it is stated, was rapidly reduced to two minutes by several intravenous injections of sodium citrate.

borne in mind throughout, but in a severe case this possibility should not make the operator too conservative. Intranasal manipulations may for a time increase the tendency to epistaxis but once the offending lesion or lesions have been located they can be destroyed. This should be the goal of both patient and operator.

Needless to say, nothing of decisive value can be done for such rare cases as the one of Osler's with lesions in the stomach or that of Goldstein's with cortical telangiectases. Metrorrhagia caused by telangiectases might however be amenable to local treatment. The hemorrhages themselves require the usual emergency treatment, whether it be for epistaxis or bleeding lip or tongue. Measures designed to influence coagulation time of blood are of no value.

CASE REPORT.—Mrs. M. C., aged thirty-seven years, a Russian Jewess, was admitted to the Woman's Medical Ward, on the service of Dr. Alfred Stengel, July 1, 1922. She was referred with diagnosis of "chronic purpura hemorrhagica," for which she had been given calcium lactate internally and thromboplastin by hypodermic injection over a period of many months without improvement.

Chief Complaint. Nose-bleeds, spots on lips and tongue, weakness, and swelling of the feet.

History of Present Illness. The patient has had occasional epistaxis as far back as she can remember but until three or four years ago the attacks were infrequent and easily controlled. Since this time however they have increased greatly in frequency and severity—averaging one a week and sometimes she has had daily attacks for a week or more at a time. The epistaxis seems to be chiefly left sided and is frequently nocturnal in occurrence. She is now very weak and nervous, has lost 15 pounds in eight months and has palpitation and dyspnea on slight exertion in addition to headache, vertigo and some edema of ankles.

Three years ago she had the first attack of bleeding from her tongue. She consulted a doctor who called her attention to small purplish spots on her tongue and lips. She had never noted any of these before. Two years ago she found that similar spots were appearing on her forearms and fingers. There have never been any spots on the face, trunk or lower extremities. All the spots have remained unchanged.

In addition to epistaxis she has had four attacks of moderate bleeding from the tongue, and from puberty at fourteen years of age until marriage at seventeen she had considerable metrorrhagia and menorrhagia. Since her first pregnancy, however, she has had very little of this form of hemorrhage and has passed through five uneventful labors. She has had no hemoptysis, no hematemesis, no hematuria, no melena and she does not bleed abnormally from trauma. No painful swelling of joints. No abdominal cramps. No glandular swellings. No itching of skin. No jaundice. Appetite

fair. Some heartburn after eating. No vomiting. No hemorrhoids. No dysuria. No nocturia.

Past Medical History. Negative.

Family History. Patient is mother of five children living and well, except that one (her nine year old son) has frequent nose-bleed. The patient has one sister and one brother in Russia of whom she knows nothing. She lost one brother who died of "tuberculous hemorrhages from the throat." He, too had spots on his lips. The patient's mother died of "heart disease" at the age of forty-three years, and she had frequent epistaxis and spots on her face and forearms. One brother and one sister of the patient's mother also had frequent epistaxis, and the patient recalls having heard that her maternal grandfather had the same trouble.

Physical Examination. Blood-pressure, 115–75; temperature, pulse, respirations are normal. The patient is a fairly well-nourished white woman, aged about thirty-five years. She is pallid and of sallow complexion. Speech, mentality, station, gait and bodily movements normal.

Head. Rhinoscopy reveals old blood clot in left lower fossa. Both lower turbinates congested. The left side of the nasal septum presents a single dilated venule and several minute red spots which blanch on pressure. Similar spots are seen in the mucosa of both inferior turbinates.

Ears. Negative; no spots on tympanic membranes.

Mouth. The lips and tongue present similar spots, some of which are raised papules, and all of which disappear under pressure of a glass slide. Pharynx negative.

Eyes. Negative; no conjunctival telangiectases; eye grounds normal; marked hyperopia with astigmatism.

Neck. Negative.

Thorax. Negative. Heart and lungs normal. No spots on trunk.

Abdomen. Negative except that both kidneys and the sharp, non-tender edge of the spleen can be readily palpated on deep inspiration.

Upper Extremities. Negative except for a few small macular and papular telangiectases in the skin of forearms and fingers.

Lower Extremities. No telangiectases; slight edema of ankles and varicose veins under right knee.

Neurological Examination. Negative.

Pelvic Examination. Negative; cervix and vagina show no telangiectases. Uterus and adnexa normal. No intra-uterine bleeding on passage of a sound.

Blood Count. July 2, 1922. Erythrocytes, 4,000,000; hemoglobin, 75 per cent; leukocytes, 7000; neutrophiles, 65 per cent; lymphocytes, 27 per cent; large mononuclears, 2 per cent; transitionals, 4 per cent; eosinophiles, 2 per cent. No myelocytes. No abnormal changes in the erythrocytes.

Urinalysis entirely normal; acid; specific gravity, 1025.

Bleeding time, one minute; coagulation time, five minutes (capillary); six minutes (Bogg's).

Fragility test: Hemolysis begins at 0.425—complete 0.325.

Blood platelets varied from 112,000 to 280,000.

Blood Wassermann negative.

Clinical Notes. July 5, 1922. Had slight bleeding from mouth which patient thought was from her gums but on examination was found to come from telangiectatic spot on right margin of tongue.

July 6, 1922. Dr. H. K. Pancoast destroyed the more prominent lesions of tongue and lips with electric desiccator needle using cocaine anesthesia locally.

July 10, 1922. Treatment of intranasal lesions by chromic acid cauterization begun by Dr. David Husik.

July 12, 1922. Epistaxis last night—controlled with difficulty by packing soaked in thromboplastin.

July 14, 1922. The patient's nine year' old son reported for examination. He has a dilated venule in septal mucosa on left side and a typical telangiectatic spot on upper lip and one on left forearm. No spots on tongue. Spleen not palpable. Hemoglobin, 85 per cent. Platelets, 150,000. He has had frequent nocturnal epistaxis since age of two years.

July 18, 1922. Patient discharged. To continue treatment in nose and throat dispensary.

August 11, 1922. Readmitted. Patient did not report for treatments owing to illness in her family. Has had considerable epistaxis and is weak and nervous. "Rest cure" in ward for a few days. Has had no recurrence of lingual bleeding since desiccation of the lingual spots, which show no evidence of recurrence.

October 15, 1922. Patient has been reporting regularly to Dr. Husik for past few weeks. He has destroyed all visible lesions in left nostril. No epistaxis for two weeks.

December 10, 1922. Patient has had no trouble for over two months. Apparently cured. She has gained 10 pounds in weight and says she feels "fine."

Summary and Conclusions. 1. Hereditary hemorrhagic telangiectasia is characterized by the formation of localized dilatations of capillaries occurring, for the most part, during youth in the nasal mucosa. The telangiectases may appear elsewhere on the cutaneous mucosal and epithelial surfaces, though usually not until adult life is reached, and may be the seat of hemorrhages wherever they occur. The rupture of these vascular defects results from slight traumatism or from local congestion, vasomotor or irritative, and this explains the recurrent hemorrhages, particularly the epistaxis so prominent in this disease.

2. There is no demonstrable "hemorrhagic diathesis" in this disease.

3. Atavism is a factor which has not been sufficiently emphasized.

The literature discloses 212 afflicted individuals belonging to thirty families exhibiting the disease in classical form. There are seven instances of atavistic inheritance among these. The literature also contains reports of similar, though apparently non-hereditary cases which should be classed as atavistic examples of the disease.

4. The absence of characteristic family history does not preclude the diagnosis of this disease, which should be borne in mind in any case presenting obscure hemorrhagic phenomena. Especially suggestive is the analogy between this disease and certain cases of so-called essential hematuria, particularly the "hereditary hematuria" group.

5. Symptomatic cure can be accomplished for the majority of these patients by careful and, if necessary, repeated cauterization of the offending telangiectases.

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AN EXPERIMENTAL STUDY OF THE MELTZER–LYON TEST, WITH COMMENT ON THE PHYSIOLOGY OF THE GALL-BLADDER AND SPHINCTER VATERI.*

By Joseph S. Diamond, M.D.

NEW YORK.

Introduction. The historical footnote to the article in which Meltzer[1] discussed some phases of the physiology of the gall-bladder, particularly the law of contrary innervation, has given rise to considerable clinical and experimental work on the physiology and pathology of the biliary tract. In this footnote, he casually suggested the application of magnesium sulphate to the mucous membrane of the duodenum as a clinical method of therapy to dilate the sphincter, situated at the common duct, in cases of obstructive jaundice, whether of catarrhal origin or calculus blockage, thus utilizing the general principle of the magnesium radical as a depressor to smooth muscle and stimulant to the inhibitory fibers.

This suggestion visualized in the mind of Lyon,[2, 3, 4, 5] a definite physiological process with a definite train of events, which he utilized in the diagnosis and therapy of biliary diseases. The technic of the Lyon method is at this time too well-known to require any detailed résumé. Suffice it to mention that the introduction of about 50 cc of a saturated solution of magnesium sulphate into the duodenum by means of a duodenal tube, is followed, within a few minutes, by a deeply pigmented bile which Lyon has called the "B'' bile. This "B'' bile is usually of a rather viscid consistency and varies in quantity ordinarily between 30 and 60 cc. It is followed by a lighter, less viscid flow.

Lyon, noticing the similarity of the "B'' bile to the contents of the gall-bladder as to color and viscidity, assumed that the "B'' bile is gall-bladder bile. The validity of the Lyon method of therapy and diagnosis depends largely in attributing to the gall-bladder the origin of the dark "B'' bile. It is this particular phase of the problem which has been of greatest interest. To prove the validity of these views a series of animal experiments were undertaken which differed from those of Crohn,[6, 7] in enabling us to carry on repeated observations for longer periods with the animal in the waking state.

The questions that present themselves for elucidation are as follows:

1. Does the deeply pigmented viscid bile originate in the gall-bladder?

* The animal experiments herein recorded have been carried out in Prof. Bickel's Laboratory at the Pathological Institute of the Charite Hospital, Berlin, during the winter of 1921–1922. The surgical operations were performed by Prof. Bickel, for whose kind assistance the writer feels greatly indebted.

2. Does the gall-bladder contract and empty its contents in the sense of any other hollow viscus, like the urinary bladder?
3. Can the gall-bladder contract at all?
4. What is the function of the gall-bladder?
5. Is Oddi's muscle a sphincter in the true sense of the word?
6. What relation, if any, does it bear to the gall-bladder?
7. Does magnesium sulphate, or any other chemical substance, produce a dilatation of the sphincter and simultaneously cause the contents of the gall-bladder to empty its contents, thus bringing into play Meltzer's law of contrary innervation?

The solution of the physiological problems that presented themselves depended on the ability to obtain gall-bladder contents in dogs with the animal in a normal waking state. Crohn conducted a series of observations on narcotized dogs, in which he introduced methylene blue into the gall-bladder and studied the effect of various mechanical and chemical effects upon Oddi's sphincter and their bearing on the gall-bladder. Later, Bassler, Luckett and Lutz[8] observed the behavior of the gall-bladder during the course of laparotomies, the surgeon holding the gall-bladder between his fingers, while magnesium sulphate was applied through a previously introduced duodenal tube. The objections, however, that presented themselves in both instances were that conclusions were drawn with the subjects under deep narcosis. The blockage of the reflexes could have been responsible for the lack of the stimulus to the gall-bladder when the ampulla of Vater was stimulated chemically by the application of the magnesium sulphate or other substances.

It occurred to me that if such observations could be carried out with the animal in a normal state the conclusions thus drawn would be beyond criticism as to interference with the reflex arc. I therefore decided to establish a duodenal fistula and at the same time to introduce a foreign substance like a carmine emulsion into the gall-bladder, and when the animal recovered from the operation to inject through the duodenal cannula various chemicals and study their effects upon (*a*) the character of bile secreted; (*b*) character of gall-bladder contents; (*c*) the character of the bile during the digestive period and during the period of rest; (*d*) the interchange of hepatic bile with the gall-bladder contents, and (*e*) duration of gall-bladder stasis.

Animal Experimentation. The operation was performed as follows: Under ether anesthesia the gall-bladder was exposed. The fundus was then grasped by a clamp and brought to the opening of the wound. The needle of a record syringe was then introduced into the gall-bladder and about 5 cc of its contents withdrawn. A carmine suspension made up to about the same consistency as the gall-bladder bile was then injected into the gall-bladder through the same needle, the quantity injected being the same

as that withdrawn. A single stitch was then introduced at the point of the puncture and the gall-bladder allowed to drop to its normal position. The second step of the operation consisted in making a duodenostomy in the second portion of the duodenum, opposite the ampulla of Vater. A metal cannula was then introduced into the duodenal opening and held in place by a double row of stitches. This cannula was then brought through the abdominal wall by a puncture with a trocar and the wound was then closed. A small cork was introduced into the opening of the cannula so that there would be no constant leakage of the duodenal contents. The animal was then permitted to recover and for several days no observations were made.

The observations were conducted as follows: The animal, with a fasting stomach, was placed upon an elevated stand, the cork removed from the cannula and the duodenal contents allowed to flow into a glass container intermittently for several minutes at a time. It invariably contained bile of a golden-yellow appearance. Microscopical examination of the centrifuged specimen of this bile did not reveal at any time the presence of carmine granules. After a number of these observations, 20 cc of a saturated solution of magnesium sulphate was injected through a soft-rubber catheter inserted into the duodenum through the metal cannula with the point directed upward. The catheter was then withdrawn and the cork promptly replaced. After an interval of two minutes the duodenum was again allowed to drain. Such observations were repeated at two-minute intervals and carried on as long as a half hour and longer. The injections were then again repeated and the duodenal contents collected and examined.

At no time was there observed the appearance of carmine macroscopically. Occasionally a few carmine granules could be found microscopically after feeding the dog. Observations were conducted daily, not only was magnesium sulphate used for intraduodenal injections, but also weak solutions of HCl and peptones. Later on we also introduced magnesium sulphate solution into the stomach of the dog by means of a stomach tube, using about the same concentration. If the duodenal stopper was removed the pylorus became patent and most of the magnesium sulphate could be made to flow out of the cannula very rapidly, almost as fast as it was introduced into the stomach. At no time did it contain any carmine. The dog at all times was in excellent physical condition with the exception of the first day or two, and later did not seem to mind the injection of the various chemicals. After about four weeks' study on the first dog, a second dog was operated upon in a manner similar to the first, but withdrawing the entire contents of the gall-bladder and refilling it with a carmine suspension (10 cc) so that the gall-bladder became moderately distended. After three days the second dog was subjected to observations similar

to those made on the first and carried on for ten days. During the fifth week a third dog underwent a similar operation, the entire gall-bladder contents being removed and substituted by carmine emulsion, this filling the gall-bladder completely. Observations similar to those described were carried out for one week. At the end of this period all of the three dogs were killed by the injection of chloroform into the heart. Death was instantaneous in each case. The periods of observations were six weeks for the first, two weeks for the second, and ten days for the third dog.

The autopsy in each case revealed no inflammatory reactions around the gall-bladder as a result of the operation. There were no adhesions present around the cystic duct that would interfere with the outflow of the contents. The gall-bladder was removed intact and when held by the fundus the contents poured out freely. The gall-bladders were found normally filled. The contents in dogs Nos. 2 and 3 were made up of practically the entire carmine injected at the time of the operation; only a small amount of bile was found in the neck of the gall-bladder. Dog No. 1, in whom less than one-half of the amount was injected, still contained a small residue of the carmine, about ½ cc, showing that within six weeks there was no complete evacuation.

Literature and Discussion. The teachings transmitted through the older text-books in physiology attribute to the gall-bladder the function of a reservoir for the storage of the bile which comes down from the liver through the hepatic ducts in the fasting state and, during the active period of digestion, is discharged into the intestine. Stress is laid upon the concentration of the digestive ingredients of the bile and that with each stage of the digestion a concentrated bile is promptly supplied. More recent views hold that the act of emptying of the gall-bladder is produced by the reflex of the acid chyme entering the duodenum which causes relaxation of the sphincter at the ampulla of Vater, and through a reflex mechanism causes the gall-bladder to empty. Mann[9] in his discussion of the function of the gall-bladder subdivided it into three heads: (1) As a reservoir for storage of bile; (2) as a secretory organ; and (3) as a regulator to the flow of bile.

Reservoir. The implausibility of the gall-bladder functioning as a storehouse becomes apparent when we consider that the total secretion of bile for twenty-four hours in a normal man may rise to 1200 to 1500 cc and the capacity of the gall-bladder is only 30 cc, one-fiftieth capacity of the total volume secreted. In common duct obstruction due to calculi one never notices distension of the gall-bladder. Similarly, in the above mentioned experiments, a clear golden-yellow bile was invariably present in the fasting state. Through familiarity with the duodenal intubation we have come to learn that the bile flow is continuous even in the fasting state and that a steady non-intermittent flow can be noticed at all times.

CONTRACTION OF THE GALL-BLADDER. Through the valuable experiments of Bainbridge and Dale,[10] wherein they study the motor phenomena and the innervation of the gall-bladder by means of a rubber balloon introduced into the fundus of the gall-bladder, and connected with a manometer which registered the variation and tone, we learn that the gall-bladder is capable of undergoing very faint rhythmical contractions and slight changes in tone. In their studies on the innervation of the gall-bladder they were able to demonstrate that stimulation of the splanchnics, especially of the right, causes relaxation in the tone of the gall-bladder, especially in the region close about the neck. Bainbridge and Dale noted that the marked increase in tone reported by Doyon[11] was dependent upon extraneous causes, especially upon the changes in the liver volume. The enlargement of the liver which is observed as a result of sympathetic stimulation caused by the intravenous injection of adrenalin simulated the gall-bladder contraction. The changes in the liver volume are merely dependent upon the rise in blood-pressure, the contrast being more marked when the animal is bled, thus producing a very low blood-pressure prior to the adrenalin administration.

The parasympathetic effect which was obtained by a stimulation of the peripheral end of the vagus, especially of the left, was a slight augmentation in the tonal rhythm of the gall-bladder as noted with the manometer. No strong contraction similar to the muscular contractions of any hollow viscus was at any time noted. Neither is there any mention made of any observation on contrary innervation in the sense of Meltzer's assertion. These observations of Bainbridge and Dale made in 1905 are in accord with those of Lieb and McWhorter,[12] who, in 1915, studied the contractibility and tonicity of the isolated gall-bladder with the aid of drugs. They found that stimulation of the parasympathetic apparatus with pilocarpine and physostigmine produced increase in tone while atropine and adrenalin caused relaxation.

One therefore finds from the painstaking research of Bainbridge and Dale and Lieb and McWhorter that the gall-bladder is incapable of muscular contraction analogous to any other hollow viscus and that it is capable of only very slight changes in tonal rhythm which would be insufficient *per se* in causing the slightest evacuation of any of its contents. Our own experiments indicate the slow admixture of bile with the foreign substance and that foreign substances may be retained for weeks in the gall-bladder though the animal be kept in a normal state and properly fed.

SPHINCTER. While it is true that a sphincter at the ampulla of Vater exists and that it is capable of a slight tone, yet no one has been able to establish, in spite of the number of experiments carried out, any relation between this sphincter and the gall-bladder. Judd and Mann[13] report that the sphincter can withstand a pressure vary-

ing from 100 to 645 mm. of water and that the normal intraductal pressure, that is the secretory pressure of the liver, can withstand 230 mm. water and that it rises in cholecystectomized dogs to 360, in which cases the common ducts increase somewhat in diameter and muscular thickness.

One cannot speak of the sphincter as bearing a direct relation to the gall-bladder when we consider its anatomical situation. It is located several inches away from the neck of the gall-bladder.

One must consider the sphincter as an organ bearing direct relation to the common duct and to the intraductal pressure, regulating the opening into the intestines according to the rate of flow as it comes down from the liver, dilating somewhat to accommodate its rapid flow, which takes place in the digestive period or contracting when the flow disappears. The contraction of the sphincter is an important function, perhaps more important than the dilatation, and may be regarded as a protective measure to inhibit the regurgitation of the intestinal contents, food, digestive enzymes, and bile back into the biliary radicals and pancreatic duct. That the papilla of Vater is capable of contraction and that the contraction is an active process can be easily demonstrated by physical, mechanical or electrical stimulation of the papilla. The slightest faradization or passing the finger gently over it will cause a visible contraction and a raising of the papilla.

In our experiments where the papilla of Vater was daily bathed with magnesium sulphate and other chemicals for a period of weeks, we could not produce any reflex effect upon the evacuation of the gall-bladder contents. Neither did we see the discharge of its contents to any appreciable degree during the digestive period.

These may therefore be regarded as conclusive evidence as to (1) the absence of relation between the sphincter papilla and the gall-bladder, (2) the absence of reflex mechanism or contrary innervation between the sphincter papilla and the gall-bladder, whether (*a*) during the digestive period or (*b*) induced chemically, by magnesium sulphate, etc.

Many clinical data have recently been accumulated, particularly by Dunn[14] and Dunn and Connell,[15] where the typical ABC sequences were obtained in cases with cholecystectomized individuals, impacted cystic ducts, and in a case of hepato-duodenostomy, where the gall-bladder and the common duct and all the large biliary radicals were absent, including even the sphincter papilla where a new anastomosis was made between the remnant of the hepatic duct and the duodenum. Similar changes in the physical characteristics of the bile were obtained by these observers when the magnesium sulphate was applied to distant parts of the intestine, in one instance as far as 32 cm. into the jejunum, and in others through application into the rectum and colon. These data further tend to invalidate the relation between (1) the sphincter

papilla and the gall-bladder, and (2) the application of Meltzer's law of contrary innervation to these organs. One must look elsewhere for the cause of the changes of the physical characteristics of the bile, and therefore the utilization of Lyon's test for diagnosis and therapy of biliary pathology becomes untenable.

Conclusions. 1. The function of the gall-bladder may be regarded merely as a slight overflow receptacle in the nature of a diverticulum of the common duct, devoid of contractile powers, which is merely able to receive small quantities of bile whenever the intraductal pressure rises higher than usual, the emptying of the gall-bladder being purely a passive act dependent upon mechanical factors. It is obvious that it never empties itself completely in the manner of any other contractile hollow viscus, but that occasionally small quantities may escape.

The retention of the carmine suspension in toto for about a week without any admixture of bile with the exception of a small quantity at the neck, and the presence of some carmine in the fundus of the bladder after six weeks when only one-half of the contents of the gall-bladder were replaced by carmine, prove the slow filling and emptying, the slow interchange of bile between the ducts and the gall-bladder.

That the gall-bladder possesses no special function may be adducted: (1) From the above experiments and also from Crohn's, whose results as regards retention of foreign substances introduced into the gall-bladder for long periods at a time were analogous; and (2) from the anatomical fact that certain species of animals like the horse, elephant and others have no gall-bladder and that it may be congenitally absent in man; and (3) that no untoward results or any pathological alteration were ever noted in the vast number of cholecystectomized individuals.

2. The sphincter Vateri bears no relation to the gall-bladder, either anatomically or physiologically. It does not form part of the gall-bladder structure. It is situated several inches from the gall-bladder. The experiments carried on by the writer failed to prove through stimulation of the sphincter any effect upon the gall-bladder contraction or evacuation of its contents. The experiments were conducted with the animal in the waking state and numerous observations were carried on daily, in one dog for a period of six weeks.

Clinical observations of Dunn, where the ABC bile sequences were obtained in cholecystectomized individuals and cystic duct blockage, and in the absence of the common duct and all bile radicals where a hepatoduodenostomy existed, further tend to disprove the selective action of magnesium sulphate upon the sphincter papilla and through it any contrary innervation causing contraction and evacuation of the gall-bladder.

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REVIEWS.

COLLECTED PAPERS FROM THE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE. VOL. I, 1921. Pp. 1079; 347 illustrations. St. Louis: C. V. Mosby Company, 1923.

EXCELLENT as are the individual articles contained in this book, interesting as they may have been when they appeared in current literature, there seems to be little excuse for the gathering of them together in book form. Each article is available in the journal of its original publication and it would be referred to in that place by anyone desiring to read it. One can scarcely picture any physician purchasing the present volume, and indeed it will be of little value even to a medical library. The object of such a publication as is stated in the preface is to present primarily to the alumni of the institution the most recent contributions from that institution to medical research and experience. This object is certainly achieved and the contents of the book should make the alumni proud of the institution. P.

TUBERCULOSIS IN INFANCY AND CHILDHOOD. By J. CLAXTON GITTINGS, M.D., Professor of Pediatrics in the Graduate School of Medicine, University of Pennsylvania; FRANK CROZIER KNOWLES, M.D., Professor of Dermatology in the Jefferson Medical College; and ASTLEY P. C. ASHHURST, M.D., Associate Professor in Surgery, School of Medicine University of Pennsylvania. Pp. 273; 23 illustrations. Philadelphia: J. B. Lippincott Company, 1922.

THIS book is composed of a series of lectures given at the Children's Hospital under the auspices of the Philadelphia Pediatric Society. It is destined to give to the general practitioner in a short comprehensive way all the essential elements necessary in recognizing and treating tuberculosis in all its phases in early life. The subject matter is clear and concise, beginning with a general chapter in which are considered the various subjects as: Types of tubercle bacilli, and their relative importance, childhood infection and immunity, modes of infection and so on. Other chapters are

devoted to the importance of a careful history, pointing out salient focal and constitutional symptoms combined with the physical examination. The value of various tuberculin tests is given. The various forms of tuberculosis found in early life are dealt with in full, including a separate chapter upon tuberculosis of the skin and another upon tuberculosis of bones and joints. The chapter upon miliary and generalized tuberculosis and meningitis is especially full and comprehensive, as well as the chapter upon the treatment of the tuberculous child. The book is well written and well deserving of a prominent place in the contributions upon tuberculosis. It is of special value to the general practitioners for whom the book was designed. K.

DUFF HOUSE PAPERS. VOL. I. Edited by EDMUND I. SPRIGGS, M.D., F.R.C.P. Pp. 387; 197 illustrations. London: Oxford Medical Publications, 1923.

THE publishing in book form of scientific articles which have already appeared in current literature may be desirable from the point of view of the laboratory or institution from which they originated, but can be of little interest or value to the profession at large or even to medical libraries. The collection in book form serves to demonstrate the activities of the institution and can be employed for distribution to benefactors but the gathering together of heterogeneous articles in a book can serve no useful scientific purpose. In the volume under discussion there are articles on the gastro-intestinal tract, diabetes, pancreatic insufficiency, sprue, etc. P.

PRINCIPLES AND PRACTICE OF X-RAY TECHNIC FOR DIAGNOSIS. By JOHN A. METZGER, M.D. Roentgenologist to the School for Graduates of Medicine, Medical Department, University of California, Southern Division, Los Angeles. Pp. 144; 61 illustrations. St. Louis: C. V. Mosby Company, 1922.

IN this manual the author has concisely presented some of the fundamentals of roentgen-ray technic. The photographic reproductions are unusually good. These with the aid of the text gives one a very good idea as to the positions in which various parts of the body are examined. Most of the positions are more or less standardized, but in others, the author has presented his own technic, and these may vary somewhat with different workers. In addition to the preparation of the patient, the author gives his table of exposure for each examination, which will be of considerable help to one unfamiliar with this type of work. P.

CEREBROSPINAL FLUID IN HEALTH AND IN DISEASE. By A. LEVINSON, B.S., M.D., Associate in Pediatrics, Northwestern University Medical School. Second edition. Pp. 267; 69 illustrations, including 5 colored plates. St. Louis: C. V. Mosby Company, 1923.

IN the four years since his first edition the author has brought his monograph up to date. Thirty-six pages and thirteen illustrations have been added. Indications and contraindications for lumbar puncture are tabulated and the method of cistern puncture is described in brief. Recent advances in chemistry of spinal fluid are incorporated in the new chapter of physico-chemical properties. The cytology is more accurately described and recent studies of diseases are added. Very little new has been added on treatment and no mention is made of the therapeutic value of spinal drainage. The bibliography has also been brought up to date. This monograph is a valuable one to the laboratory worker, student and clinician alike and enables one to obtain all the essential information of the subject. B.

GRUNDRISS DER HYDROTHERAPIE. By DR. WALTER KREBS, Chefarzt des Landesbades der Rheinprovinz in Aachen. Second edition. Pp. 149; 10 illustrations. Bonn: A. Marcus & E. Weber, 1923.

A SHORT treatise on: (1) The effect of hydrotherapy on various physiological functions (15 pages); (2) the technic of various hydrotherapeutic methods (47 pages); (3) its application in various diseases (83 pages). K.

PRACTICAL BACTERIOLOGY, BLOOD WORK AND ANIMAL PARASITOLOGY. By E. R. STITT, A.B., PH.G., SC.D., LL.D., Rear Admiral, Medical Corps, and Surgeon-General, U. S. N., etc. Seventh edition. Pp. 15 and 766; 203 illustrations. Philadelphia: P. Blakiston's Son & Co., 1923.

OF today's various laboratory manuals none could be less easily dispensed with than this one. It continues to astonish the grateful user with the amount and variety of accurate information condensed in small space and presented in easily available manner. Since its last review in this Journal (1918, **155**, 133), the volume has been increased by over 200 pages, 132 of which were added in this seventh edition. This has permitted the addition of "a summary of the subject of nutrition," a fuller treatment of methods

of immunity, the protozoa and mosquitoes, a large number of new tables, description of flocculation tests for syphilis, etc. By a typographic error in the table of contents, the pagination of Chapters XXXVI and XXXVII has not been altered from the sixth edition. K.

TONSILLECTOMY BY MEANS OF THE ALVEOLAR EMINENCE OF THE MANDIBLE AND A GUILLOTINE, WITH A REVIEW OF THE COLLATERAL ISSUES. By GREENFIELD SLUDER, M.D., F.A.C.S., Clinical Professor and Director of the Department of Rhinology, Laryngology and Otology, Washington University School of Medicine. Pp. 176; 90 illustrations. St. Louis: C. V. Mosby Co., 1923.

IT is with a great deal of enthusiasm that we welcome the writer's publication on tonsillectomy. "The Sluder operation" for the removal of tonsils has been tried and tested throughout the world, until its importance in the field of laryngology has been firmly established. It has become one of the modern standard operations and it is right and proper that its author should see to it that the proper technic be plainly set before the laryngological world. In doing this, the writer has gone carefully into the whole tonsillar question, though the surgical part of the monograph is limited to the technic of the Sluder operation and the removal of adenoids by direct visions, the latter subject being written by Dr. I. D. Kelly. A very important part of the book is the chapter on physiology and general pathology of the tonsil, written by Arthur W. Proetz. Although we cannot agree with some of the views expressed, this review of the tonsil question is really one of the most carefully written articles on the subject. One of the most impressive features of the book is the apparent study that the author has made of the literature on the subject, and the room given to the opinion of other authorities. There is a fairly complete appended bibliography. The work is profusely illustrated, the large majority being original microphotographs and drawings. We recommend this book to the beginner and to the skilled specialist; the general practitioner will find much of interest in its pages—the mature utterance of one of the world's great specialists.

W.

TUBERCLE BACILLUS INFECTION AND TUBERCULOSIS IN MAN AND ANIMALS. By ALBERT CALMETTE, Associate Director, Pasteur Institute, Paris. English translation by W. B. SOPER, Saranac Lake, and G. H. SMITH, School of Medicine, Yale University. Second edition. Pp. 714; 56 illustrations. Baltimore: Williams & Wilkins Company, 1923.

THIS is a splendid translation of a very worthy book. The author has built a monument on the subject of tuberculosis by

virtue of his intimate knowledge of the subject. It includes not only the researches of the author and his pupils, but in addition a summary of our knowledge of tuberculosis. Beginning with its history, he traces its development, and takes up every conceivable point, with the result that a complete book has been attained. The physician, the veterinarian, the laboratory investigator and the preventive worker will find the book equally important and equally suggestive of ideas. The illustrations, particularly the full color plates, are a strong asset to the text. J.

INFECTION AND RESISTANCE. By HANS ZINSSER, M.D., Professor of Bacteriology and Immunity, Harvard Medical School. Third edition. Pp. 666; numerous illustrations. New York: Macmillan Company, 1923.

ALTHOUGH Prof. Young's chapter on Colloids has been omitted from this edition, it is eighty-one pages longer than the second, which appeared in 1919. This is brought about both by small additions throughout the book and by the revision and increase of the chapters on anaphylaxis and practical therapeutic methods and theories, with new chapters on iso-antibodies and the nature of antibodies. In spite of a certain obscurity of style, which makes a complex subject doubly difficult to read, this new edition should be welcomed by student and teacher alike. K.

THE ANTIQUITY OF DISEASE. By ROY L. MOODY, Associate Professor of Anatomy in the University of Illinois. Pp. 148; 36 illustrations. Chicago: University of Chicago Press, 1923.

ONE of the few complaints to be made about this latest contribution to the University of Chicago Science Series is that it is much too short. Although the author is a well-known authority on the subject (he is also the editor of Ruffer's *Studies in the Palæopathology*) and has selected wisely, it has not been possible, and probably not even attempted, to give a clear picture of the comparative pathology of the ages within such small scope. The glimpses afforded into the beginnings of disease, fossil pathology and primitive human pathology and surgery, should, however, furnish ample stimulus to the reader to go further into this fascinating field.

The pictures of the oldest known bone tumor (a hemangioma of a dinosaur) and oldest known fracture (a transverse break of the radius of a Permian reptile) inevitably lead one on to neolithic

evidences of fracture and bone tuberculosis, prehistoric trephines, early Egyptian spondylitis, schistosomiasis, splenomegaly, described in the final chapters. It is interesting to know that although bacteria are among the oldest inhabitants of the earth, and may even have initiated life on this earth by being carried from distant planets on meteorites, they were not for ages connected with disease. "Disease was not present in the earliest times of the earth's history" and "it is only after the great Coal Period that infected wounds are found." Surely more attention to such studies and to the cognate subject of the history of medicine will not only afford pleasant reading to the modern medical man, but will develop a perspective capable of rendering material aid in defeating the various cults that now hamper medical practice.

K.

OUTLINES OF MEDICAL ZOÖLOGY. By R. W. HEGNER, W. W. CORT and F. M. ROOT, of the Department of Medical Zoölogy, School of Hygiene and Public Health, the Johns Hopkins University. Pp. 175; 21 plates. New York: Macmillan Company, 1923.

THIS small hand-book is intended for the use of public health officers, students and physicians, especially those practising in tropical or semitropical countries. For greater simplicity, many of the lesser known species of parasites have been omitted. Its three parts consider: (1) Protozoa parasitic in man; (2) worms parasitic in man; (3) arthropods of medical importance. The material is well presented and should prove useful to workers in this field.

K.

BACTERIOLOGY (A STUDY OF MICROÖRGANISMS AND THEIR RELATION TO HUMAN WELFARE). By H. W. CONN, PH.D., formerly Professor of Biology at Wesleyan University and Bacteriologist of the State Board of Health of Connecticut; and HAROLD J. CONN, PH.D., Soil Bacteriologist at the New York Agricultural Experiment Station. Pp. 441; 48 illustrations. Baltimore: Williams & Wilkins Company, 1923.

THE authors present the scope of the book in a descriptive subtitle as "Discussing the History of Bacteriology, the Nature of Microörganisms and Their Significance in Connection with Pathology, Hygiene, Agriculture and the Industries." The history of bacteriology is presented in a most interesting manner and should tend to give the beginner in bacteriology the proper perspective. The various activities of microörganisms, their relations to the

fertility of the soil to the various industries and to Public Health are discussed in a style which will hold the reader's attention and with detail enough to broaden the viewpoint and to win the student's profound respect for this young science. A section on Pathogenic Microörganisms records briefly the facts necessary for a first acquaintance with this subject. The introduction of Plant Bacteriology and its relation to certain plant diseases rounds out the work. The book is well adapted for collegiate courses in general bacteriology. S.

A Manual of Artificial Respiration. By Capt. G. R. G. Fisher, with the American Red Cross overseas during the World War; Director, Bureau of First Aid, Northern Division, A. R. C.; Director of Accident Prevention and Instructor in First Aid to Industries and Civic Organizations of the City of Omaha, Nebraska. Pp. 80; 22 illustrations. Boston: The Stratford Company, 1923.

This small brochure will give to the teachers of first aid a manual which can be used for a text-book in teaching artificial respiration. It is well illustrated and the subject matter is accurately presented. M.

Chronic Fatigue Intoxication. By Edward H. Ochsner, B.S., M.D., F.A.C.S., Attending Surgeon, Augustana Hospital; President-elect, Illinois State Medical Society. Pp. 143. New York: G. E. Stechert & Co., 1923.

The author takes for his theme the chronic fatigue intoxication, a chronic systemic disorder, which is produced as a result of accumulation in the tissues of excessive amounts of fatigue material. In the monograph he proceeds to show how the present-day individual, under the stress and strain of modern life, may develop a large number of symptoms which manifest themselves in as many ways as such a pleomorphic disease as syphilis, and which will eventually lead to a large variety of chronic degenerative diseases. The appearance of a book such as this from the pen of a surgeon should not be considered as a reflection on the internist, but rather it should rebound to the honor of one who has the ability to appreciate and to recognize this heretofore inadequately described affliction. M.

PROGRESS

OF

MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Cause of Death in Intestinal Obstruction.—BRINGLE (*Lancet*, 1923, **205**, 63) says that cause of death in intestinal obstruction is still a subject for debate. Three theories have been advanced: infection; absorption of toxins from the obstructed intestines; and depletion of systemic circulation and cerebral anemia. Research work has shown that the principal factor in causing death in intestinal obstruction is a toxin which is developed chiefly in the duodenum, and although not absorbed from the normal intestine, is absorbed under the conditions which prevail in obstruction. The exact chemical composition of the toxin is still under dispute, but it is almost certainly of the nature of the toxic bodies derived from protein disintegration. The exact mode of production of the toxin is also undecided but probably the presence of pancreatic secretion, and in lesser degree the activities of bacteria are necessary for its production. Clinical observations and experience agree with these experimental findings.

Radiography in the Examination of the Urinary Tract.—SUTHERLAND (*Jour. Radiol.*, 1923, **4**, 221) says that much interest has been expressed regarding the findings and technic in the roentgenological examination of the urinary tract. One thousand consecutive histories were studied, in which the urinary tract had been examined roentgenologically. In these cases, a total of 75 calculi were found by cystoscopic and surgical examination, 41 in the kidney, 24 in the ureter and 10 in the bladder. The section on roentgenology reported 37 of the 41 in the kidney, 14 of the 24 in the ureter and 6 of the 10 in the bladder. Thirty-one shadows diagnosed from roentgenograms in the kidney areas as calculi or suggestive of calculi were ruled out, or were not found at cystoscopic examination. Six of the 10 calculi found in the

ureters had been reported by the section as phleboliths. Phleboliths were reported in 376 patients. Shadows were often seen in the roentgenograms of areas embracing the urinary tract, which were not seen in subsequent re-rays of the same areas. Eliminating the rare passing of a stone, the conclusion must be that these shadows were cast by small concretions or particles of insoluble matter in the bowels. Several cases have been seen in which small warts on the skin have cast shadows, which were difficult to distinguish from calculi. Roentgenological evidence, therefore, cannot be accepted as final, but should be checked up by urological investigation and correlated with the clinical evidence.

Chronic Mastitis.—KEYNES (*Brit. Jour. Surg.*, 1923, **11**, 89) says that the breast is a secreting gland which shows periodical activity from birth to menopause. The normal non-lactating breast has no outlet through the nipple for the discharge of its secretions. Secretion must, therefore, be balanced normally by reabsorption. Chronic mastitis is manifested by dilatation of ducts and acini, accumulation in them of the products of epithelial activity, infiltration with lymphocytes, fibrosis and epithelial changes. Distribution of all these is very erratic. Chronic mastitis, more common in women, first appears in second decade, but is most often seen in the fifth. Chronic mastitis is not bacterial in origin, toxemic or traumatic. The cause of chronic mastitis is probably to be found in chemical irritation, due to stagnating secretions and epithelial débris. Chronic mastitis, though very often associated with carcinoma, has not been proved to be pre-cancerous.

A Case of Heart and Respiratory Failure in High Spinal Anesthesia (Saved through Heart Massage).—PHILOPOWICZ (*Zentralbl. f. Chir.*, 1923, **24**, 961), a lawyer, aged sixty-five years, showed signs of hematuria of five years standing, with marked myocarditis, arrhythmia, deep bronchitis, and emphysema. The left kidney was involved by an immovable mass, the size of a child's head. The urine showed macroscopical blood. Hypernephroma without evident metastasis was the diagnosis. General anesthesia was contraindicated, local anesthesia was not feasible in this individual case; spinal anesthesia with stovaine and strychnine alone remained. During the abdominal opening, the patient took one deep breath, and did not regain heart action and respiration after injection of the usual restoratives. The writer grasped the apex of the heart, and gave routine massage. After one minute, the heart began to beat slowly and faintly; gradually, respiration was restored, at first Cheyne-Stokes in type. With an experience of 2000 cases of spinal anesthesia, this was the author's first irregularity. The operation was completed and uneventful convalescence occurred.

End-results in Malignant Disease of the Testes.—COLEY (*Ann. Surg.* 1923, **78**, 370) says that the number of permanent cures following surgical removal of the testicle for malignant disease is comparatively small, the proportion being not over 5 to 10 per cent. This number of cures, in his opinion, is not sufficiently increased by the radical operation of removal of the retroperitoneal glands by the abdominal route, to warrant the very considerable risk of such an operation. Long continued systemic treatment with the mixed toxins of erysipelas and

Bacillus prodigiosus, combined with thorough radiation of the abdomen and supraclavicular glands by radium or roentgen-rays offers a far better hope of permanent cure than any form of operative treatment alone. If one waits after operation until a recurrence has taken place, marked regression of these recurrent tumors and in some cases complete disappearance may be expected from the radium treatment. In the great majority of the cases the regression or disappearance will prove only temporary and death from extension of the disease will occur.

Metastatic Hypernephroma.—GIBSON and BLOODGOOD (*Surg., Gyn. and Obst.*, 1923, **37**, 490) say that hypernephroma is a comparatively rare condition. Bone is a tissue of predilection for this tumor. The pathogeny of the hypernephroma is still *sub judice*. Metastasis to bone is chiefly *via* the blood stream. The bony metastasis is sometimes the only metastatic focus. Complete skeletal roentgenographical examination should be made in every suspected case. While mainly a lesion of later middle life, it is found in the young. The malignancy of the condition varies enormously. A solitary bone metastasis may be extirpated with good ultimate result. In the presence of cachexia or multiple bone metastases, palliative measures only are advisable.

Quantitative Studies in Syphilis from a Clinical and Biological Point of View.—FORDYCE, *et al.* (*Am. Jour. Syph.*, 1923, **7**, 444) says that analyses of the blood for its arsenic content after intravenous injections of silver arsphenamine were made in 299 specimens obtained from 214 patients. It was found that 56.4 per cent of the arsenic injected localizes outside the blood stream immediately after completion of the injection. Observations made at intervals of from five minutes to one day show that there is a gradual lowering of the arsenic equilibrium in the blood based on average values. Observations made after a period of one day show first a marked increase in arsenic content, and then a gradual diminution at later intervals based on average values.

Chancre of Lip.—PAROANGIAN and GOODMAN (*Am. Jour. Syph.*, 1923, **7**, 563) cited a number of case histories showing the difficulty of diagnosis in chancre of the lip. As the authors see the problem, the physician first consulted has the ultimate fate of the case in hand. If syphilis is not suspected, and the cases cited seem to prove that it is not, the patient goes through the generalized period of syphilis, and all that pertains to it. The benign appearance of early lip chancre is certainly deceptive, or else the physician is loath to consider the possibility of such a diagnosis. In most instances, the picture of lip chancre as ordinarily illustrated in text-books seems a terrible lesion indeed, and one which could never be overlooked. Unfortunately, the lip chancre of syphilis does not always follow the text-book, and as the author's photographs show, many a harmless lesion harbors the spirochete of syphilis, and unless checked by the proper treatment, the course of syphilis runs on. The dark field and the Wassermann, but above all clinical acumen and experience are needed for the diagnosis and ultimate abatement of the process of syphilis in the patient with lip chancre.

THERAPEUTICS

UNDER THE CHARGE OF

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NEW YORK,

AND

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The Administration of Insulin by Inunction.—As a result of experiments on rabbits, TELFER (*Brit. Med. Jour.*, April, 1923, p. 715) concludes that insulin can be introduced into the blood stream by inunction. This method of administration necessitates the use of much larger quantities of the drug than those required to produce comparable effects by subcutaneous injection; however, the results suggest that in this method crude insulin extracts might be utilized. As the cost of isolating the drug in a pure and active state for the purposes of hypodermic medication is so great as to restrict seriously its application on a large scale, it is possible that more liberal use of cruder materials might with advantage be made by means of inunction.

Serological Factors of Natural Resistance in Animals on a Deficient Diet.—SMITH and WASON (*Jour. Immunol.*, 1923, **8**, 195) state that the sera from animals which had been maintained upon a rickets-producing diet show certain differences when compared with sera from normally fed animals. The outstanding feature is the marked difference in the bactericidal titers; values for the most active sera among the rachitic rats being well below the lowest values secured for the normal animals. The complement titrations show but little variation, and there appears to be little if any correlation between complementing activity and the bactericidal values of the serum. The phagocytic indices, while subject to considerable variation within each group, appear in general somewhat lower among the animals fed upon the deficient diet. It is of particular interest that these serological titrations upon the group of rats which had been upon a deficient diet failed entirely to show any consistent difference which could be correlated with the anatomical findings reported by Powers (*Johns Hopkins Hosp. Bull.*, 1922, **33**, 125). Both groups, those which actually showed rickets and those which, because of radiation, failed to show rickets, were essentially alike in regard to the reactivity of their sera. It is not suggested that these changes may be fundamental or that they may be directly associated with the defective diet. It is indeed much more probable that they are indirect, being dependent upon a modified cellular activity induced by failure to provide a proper regimen. Observations quite similar to those have been made upon a large series of rats which have been put upon defective diets in various respects. In not all cases have the results been comparable to those here reported, but the general outcome of the experiments has been quite analogous to the findings in this particular series.

Etiology of Dengue Fever.—Chandler and Rice (*Am. Jour. Trop. Med.*, 1923, **3**, 233) describe an epidemic of dengue of unprecedented proportions originating in Galveston in June, 1922, which spread over all of eastern and central Texas and into neighboring states. Between 500,000 and 600,000 cases were estimated to have occurred in Texas. The authors state that the organism of dengue, shown by previous workers to be a filtrable virus in the blood plasma, has been suspected of being a Leptospira on account of a supposed relationship of the disease to yellow fever. This relationship is probably overemphasized. Dark-field examination of blood smears, inoculations into guinea-pigs, mice and monkeys, and attempts to cultivate the organism in media used for Leptospiræ, all gave negative results. Negative findings, in blood, in inoculated animals (particularly guinea-pigs), and in cultures; the usual absence of liver and kidney involvements; the fact that the relationship of dengue to yellow fever has been overemphasized; and the viability of the virus in blood kept in an ice chest after removal from the host (according to Cleland, Bradley and MacDonald) led the authors to believe it improbable that the organism of dengue is a Leptospira. Previous experimental work and epidemiological evidence point to *Aedes ægypti* (*Stegomyia fasciata*) as the principal transmitter of dengue, this species being replaced principally by *Aedes* (*Stegomyia*) *scutellaris* in Formosa. *Culex quinquefasciatus* (*fatigans*) has been incriminated on very slender evidence. The Texas epidemic was accompanied by an unprecedented scourage of *Aedes ægypti*, and the epidemiological evidence points very strongly to the agency of this mosquito in transmission, and suggests that *Culex quinquefasciatus* played a very minor part, if involved at all. Transmission experiments carried out with *Aedes ægypti* were successful in 4 out of 6 cases; the mosquitoes succeeded in transmitting the disease in from twenty-four to ninety-six hours after feeding on patients in the second to fifth days of the disease. The incubation period in experimentally infected cases, both when bitten by infected mosquitoes and when inoculated with a patient's blood, varied from four days and two hours to six days and twelve hours.

Indices of Nutrition.—Clark, Sydenstricker and Collins (*Pub. Health Rep.*, 1923, **38**, 1239) summarize an extensive and apparently carefully made study as follows:

1. For the purpose of comparing different indices of nutrition, a group of 506 children who had the following qualifications were selected from much larger numbers: (*a*) Native white of native parentage and native grandparents; (*b*) no physical defects; and (*c*) nutrition "good" or "excellent" as judged from clinical evidence.

These children were selected after careful physical examination as being in good health so far as the medical examiner (United States Public Health Service) could determine.

2. Three standards of weight were applied to them. It was found that according to the Wood standard (height-weight-age tables), 20 per cent of these children were more than 10 per cent underweight; according to Dreyer's standard (stem length and chest circumference tables), 13 per cent of the children were more than 10 per cent underweight; and according to Pirquet's "pelidisi" method, 17 per cent had pelidisi of 94 or less and were underweight according to this standard.

3. A cross tabulation was made to ascertain whether children underweight according to one standard were underweight according to other standards. Although the percentage of children who were underweight did not vary greatly when different standards were applied (13, 17, and 20 per cent), many individuals classed as underweight by one standard were classed as normal or, in a few cases, overweight, by one or both of the other standards. Out of 506 children, 210 were classed as underweight by one or more of the three standards used; of these 210 cases, all three standards agreed on 15 cases as being underweight.

These children were selected as the best specimens of health that could be found among school children. In spite of this fact, one-fifth of them were underweight according to the standard most frequently used in school health work in the United States.

Physiological Effects of High Temperatures and Humidities With and Without Air Movement.—SAYERS and HARRINGTON (*Pub. Health Rep.*, 1923, **38**, 1616) made an experimental study of this subject which is summarized by the authors as follows:

A. Remaining at rest in saturated air at 91½° F. for one hour,

With no air movement caused—

1. An increase in body temperature;
2. A moderate increase in pulse-rate;
3. Profuse sweating;
4. After effects of dizziness and weakness.

With air movement caused—

1. Slight or no increase in body temperature;
2. Slight increase in pulse-rate;
3. Slight perspiration;
4. No after effects;
5. No ill effects at any time; but the noise of the fan was annoying.

B. Remaining at rest in saturated air at 95° F, for one hour,

With no air movement caused—

1. An increase in body temperature;
2. A marked increase in pulse-rate;
3. Very profuse sweating, clothing being saturated with perspiration and sweat in shoes of all subjects;
4. Dizziness on movement, and increase in depth and rate of respiration (puffing somewhat on slight movement); chilly sensations in some subjects.

With air movement (250 to 600 linear feet per minute) caused—

1. Slight or no rise in body temperature;
2. Slight or no rise in pulse-rate;
3. Profuse sweating, but not sufficient to wet all clothing;
4. No untoward symptoms in subjects other than profuse sweating.

C. Remaining at rest in saturated air at 96° F., still and moving, caused the subjects to experience symptoms practically the same as those felt in still or moving saturated air, respectively, at 95° F.

D. Remaining at rest in saturated air at 98½° F. for one hour,

With air movement caused—

1. An increase in body temperature;
2. An increase in pulse-rate (in one case to 183);
3. Very profuse sweating, clothing being saturated (sweat could be poured from shoes);
4. Dizziness on movement. All felt that little work could be done at this temperature and that the conditions were much worse than in moving saturated air at 95° F., but not as bad as moving saturated air at 100° F.

E. Remaining at rest in saturated air at 100° F.,

With no air movement caused—

1. A marked rise in body temperature, which reached 102.3° F.;
2. A marked rise in pulse-rate, varying in different subjects more 152 to more than 175;
3. Profuse sweating, the shoes being partly filled with perspiration;
4. Early appearance of dizziness, weakness, and persistence of symptoms for about one hour after test. The test was very trying.

With air movement (200 to 800 linear feet per minute) caused—

All the above symptoms, and no subject remained a full hour.

The untoward effects upon man of almost saturated air with temperature above 90° F. and below 98° F. are much less when the air is moving than when it is still. Further, the output or work that can be done is greater when the air is moving than when it is still, with the above temperature and humidity.

No beneficial effects were found by moving saturated air at 98.6° or 100° F., even at high velocities; and there was apparently some disadvantage.

A Possible Explanation of the Absence of Bubonic Plague in Cold Countries.—ROBERTSON (*Pub. Health Rep.*, 1923, **38**, 1519) concludes his study as follows:

"The more obvious conclusions to be drawn from this discussion and these tables are as follows: (1) Bubonic plague is essentially a disease of hot climates, and, having been introduced into tropical countries, it tends to persist indefinitely; (2) outside of the immediate Tropics, this disease is rather definitely limited in the extent to which it will spread; (3) in countries with a mean midwinter temperature of 45° F. or below, bubonic plague is occasional, accidental, and distinctly self-limited, and it seems possible for it to occur in the colder regions only for short periods under unusual conditions.

"This study appears to me to sustain the deduction that the seasonal prevalence of fleas regulates the spread of bubonic plague; otherwise it becomes necessary to find at least some equally reasonable explanation for the absence of bubonic plague in cold countries.

"Any estimate of the practical results that would ensue from a determination of the correctness of the theory advanced in this article and the conclusions drawn therefrom must await confirmation by an actual and comparative flea survey of any given locality."

PEDIATRICS

UNDER THE CHARGE OF
THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Cicatricial Stenosis of the Esophagus Caused by Commercial Lye Preparations.—CLERF (*Jour. Am. Med. Assn.*, 1923, **80**, 1600) reports a number of cases in which, as in practically all cases of esophageal stenosis resulting from lye preparations, an analysis of the circumstances attending the ingestion of the alkali revealed several points of interest. The swallowing was practically always accidental, the lye, in powder or solution, having been left in reach of the child, or put on the kitchen shelf with other containers and mistaken for one of these. Sometimes it was a residue adhering to a cup which had been used for measuring the lye. This apparent carelessness was due to a lack of knowledge of the highly poisonous nature of all lye preparations. Since lye may be purchased anywhere, and since the labels on the containers either have no poison or warning notice, or if present is inconspicuous, it is seen that education as to the poisonous nature of lye is only by bitter experience. It seems difficult to understand why necessary legislation has not been provided to prevent these sad occurrences by adequate notice on the label. Similar precautions as are used for other poisons could be taken with lye to warn the public of the highly poisonous nature of these substances. Then it would be placed beyond the reach of children.

Clinical Study of Thirty Cases of Muscular Dystrophy.—FUNSTEN (*Jour. Bone and Joint Surg.*, 1923, **5**, 190) analyzed 30 cases, 4 of which were of the juvenile form, coming on at the ages of twelve, fifteen, eighteen and twenty-one years, and usually starting as the upper girdle type. The other 26 were of the infantile form, and more frequently started as the girdle type, the weakness being noted in the lower limbs, with difficulty in getting up from the floor, and in going upstairs. Stumbling, lordosis, waddling gait and the loss of reflexes were the characteristic symptoms. Twenty-four of these were of the infantile type, either the hypertrophic or the atrophic forms. There were 2 cases of the fascio-scapulo-humeral type. Seven cases were beyond the walking stage and had various contractures. Twelve cases were treated for from four weeks to three months with various glandular extracts without any appreciable effect. Seven cases were treated with calcium lactate and 11 with massage and exercises with or without glandular treatment. It is felt that the calcium lactate was of some benefit. Wassermann tests were made in 14 cases and were negative. The microscopical blood picture was normal in the 6 cases examined. The reflexes were either absent or greatly diminished in all cases, with the exception of the cremasteric and abdominal reflexes, which as a rule were present. Microscopical examination of the muscle made in 4 cases showed the fibers to be pale, with diffuse areas of granular degeneration and vacuolization. There were also areas of

infiltration between the muscle fibers. The striations were present, except in a few places where complete degeneration had taken place. Of this series of 30 cases 23 patients are known to be living, 3 are dead from intercurrent diseases, and 4 have not been recently heard from. In none of these cases was there any tangible connection between the onset of the disease and acute infectious diseases. In no case was the onset acute.

Agglutination Test for the Presence of Bacillus Diphtheria in Field or Mixed Cultures.—FITZGERALD and DOYLE (*Jour. Am. Med. Assn.*, 1923, **80**, 1675) found in 52 cultures, which on smear examination were reported positive, 47 gave a positive agglutination with one or both types of serums in dilutions up to 1 : 640. The remaining 5 cultures were not agglutinated with either serum. This was probably due to the fact that they were representatives of other agglutination types of B. diphtheriæ. Of the cultures reported negative on smear examination, 52 in all, 47 also gave negative agglutinations. The remaining 5 cultures, reported negative from smear examination, gave positive agglutinations. These discordant results are of considerable interest. The first culture was sent to the laboratory for examination for release from quarantine, and was taken from a convalescent carrier, from whom 23 cultures in all had been taken. Agglutinations were positive in dilutions of 1 : 640 with both type serums. The second positive agglutination test obtained when a negative smear was reported was with a culture for first diagnosis. This culture was taken from a student who had had a mild sore throat for several days, and had received local treatment. A second culture taken from this man some days later was negative both by smear and by agglutination tests. A third positive agglutination with a culture on which a negative smear report was given was a culture for first diagnosis. This was from a child four years of age who had had a sore throat for several days. A physician found a spot on the tonsil which he diagnosed as diphtheria. Another physician said that the disease was not diphtheria, but took a culture. This was negative by smear but positive by agglutination tests. The spot was easily removed and did not bleed and recovery took place without the use of antitoxin. Positive agglutination tests were obtained in two other instances in which the negative reports on smears were made. These cultures were taken to test for release and were from convalescent carriers. There seems to be a certain amount of presumptive evidence in these 5 cases that the agglutination reactions which were positive although smears were negative, may have more correctly reflected the true condition. Spontaneous agglutinations may occur in dilutions of 1:10 with field cultures agglutinated with specific diphtheria agglutination serums. This has not been encountered in higher dilutions. Inhibition of agglutination, the so-called prezone phenomenon was not observed in the agglutination of field cultures. This has been noted, however, in agglutinations of pure cultures of B. diphtheriæ by monotypical serums. Field cultures taken twenty-four hours previously have been employed as antigens, but the growth as a rule is less luxuriant, and the preparation of satisfactory emulsions for antigens is difficult. Rapid agglutination tests by the centrifugalization of mixtures for agglutining serums and emulsions of field cultures

have corresponded with those obtained by the technic described in detail by the authors. When the rapid method is used, results can be read about thirty minutes after the mixtures of antigen and agglutination serums are made and then centrifugalized for five minutes. This means that the entire procedure may with this method become completed within twenty-four hours after the original field culture has been taken. Cultures have been made from 4 definite clinical cases of diphtheria and the results of smear examinations, intracutaneous virulence tests and specific serum agglutination have been correlated. In these few instances there was complete correspondence in the results obtained.

Bacterial Endocarditis in Congenital Heart Disease.—CLARKE (*Jour. Am. Med. Assn.*, 1923, **81**, 371) says that there can be little doubt that the association of endocarditis and congenital heart disease is more than a coincidence. Their rather frequent association, in view of the rarity of the primary condition, lends additional weight to the statement that endocardial infections occur in hearts on previously damaged or altered surfaces. The case reported gave a history of rheumatic fever, and although no evidence of rheumatic heart disease was found post mortem, this may have contributed to his susceptibility to bacterial endocarditis. This condition is manifested in many ways, and is frequently diagnosed as typhoid fever, meningitis or malaria, and it resembles the latter condition so closely that at one time the French thought that malaria might be the cause of the condition. The predisposition of patients with congenital and acquired heart disease to bacterial endocarditis is a stumbling-block in the recognition of the disease. The knowledge of the presence of a cardiac condition is likely to lead the mind of the medical attendant away from the proper diagnosis of the fever and associated signs of infection. It should be emphasized that a fever of irregular type, of which the cause is not obvious, in a patient who has heart disease, should lead to a suspicion on endocardial infection, especially if it is long continued. Associated with this there is often seen a hemolytic anemia and acute nephritis with red blood cells and cellular casts in the urine, which make the diagnosis certain. The disease is nearly always fatal and any hope of the patient's recovery rests on the early recognition of the disease, which is probably best and earliest made by properly taken and controlled blood cultures. Recently sodium cacodylate has been used with results that lead to the hope that early cases may be greatly helped. Cyanosis is very common in congenital heart disease and may be seen in extreme grades. Anemia is important in the production of cyanosis. Polycythemia increases the tendency to cyanosis, while anemia reduces the chances of its development. The patient in this case had an anemia of severe grade of recent development on admission. While the patient had no cyanosis while in good health, its absence could not have been due to the anemia. The late urinary changes and the pathological changes in the kidneys were of interest. Hematuria has frequently been noted in subacute bacterial endocarditis, and is often considered a sign of hemorrhagic nephritis. In this case the glomerular epithelium was swollen; several glomerular loops were bloodless and disintegrated, while an active proliferation of Bowman's capsule caused crescents of swollen and

proliferating cells. No bacterial glomerular emboli were demonstrated. The absence of the emboli was unusual, as was also the absence of emboli and infarcts. In view of the numerous vegetations that were found in the heart, and their friable condition, it is impossible to explain why embolic phenomena were not present.

OBSTETRICS

UNDER THE CHARGE OF

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"Once a Cæsarean Section Always a Cæsarean Section," an Untruth. — In the *American Journal of Obstetrics*, January, 1923, page 86, Greenhill quotes this axiom saying that it is not true. He reports 4 cases of women who had been delivered by Cesarean section, 1 of whom was delivered by forceps and the other 3 gave birth spontaneously. In 3 cases the uterine cavity was explored and was found normal. Where the classic section had been done a relatively thin scar was found, and in 1 patient who had the low cervical operation no trace of a scar could be discovered. In 3 of these sections catgut only was used in closing the uterus; 1 patient had contracted pelvis; another malposition of the child; another a low placenta with hemorrhage, and the fourth a breech presentation. These were the indications for the original section. In this last case, shortly after the original section, the patient again became pregnant and was spontaneously delivered after a long and tedious labor. When her third pregnancy occurred, examination found that the scar of the original section was easily felt and indicated thinning and overstretching. The patient desired sterilization and accordingly a low fundal incision was made in the uterus, followed by the delivery of the child, the excision of portions of the tubes, and the burial of the ends of the tubes in the folds of the broad ligament. These cases indicate that, as the writer states, that Cæsarean section does not mean that in a subsequent pregnancy the operation must be repeated. In the experience of the reviewer, a patient who had a classic section for accidental separation of the placenta has since given spontaneous birth to two exceptionally large and well-formed children. This has occurred in a number of cases.

The Capillary Circulation in Eclampsia. — In the *Arch. f. Gynäkol.* (1923, **116**, 443) HINSELMANN gives the result of his study in 19 cases of eclampsia. He has collected histories of 6 other cases and in addition there have been 8 additional reported, in all 33 patients suffering from eclampsia were studied to observe the changes in the capillary circulation. As was expected the capillary circulation was much disturbed in 9 out of 10 of these patients. The phenomena were

spasm of the capillaries occurring at intervals which often entirely stopped the flow of blood. Even when these attacks were not present capillary circulation was much impaired. This condition improved when the uterus was emptied. Drugs and the extracts of glands did not influence this condition but bleeding seemed to be of some service. Pregnant women in health do not entirely escape this complication, for there is occasional contraction of the capillaries in about 5 per cent. In patients showing abnormal conditions in the kidneys this condition is three times as frequent. Clinically it has long been observed that in the presence of pronounced convulsions the general circulation is greatly embarrassed and the passage of blood through the small vessels at times ceases, probably produced by substances elaborated in the placenta. There is a tendency during pregnancy to undue irritability and frequent contraction of peripheral vessels. When the uterus is emptied in healthy patients this gradually disappears and may be one of the causes for the slow pulse seen in the puerperal period. Obviously those viscera normally most rich in blood must be most affected by this condition. As it is produced by toxins it may be most completely demonstrated in those portions of the body where the circulation is very free, the vessels small in size and readily dilating and contracting, these conditions are present in the kidneys, in the skin and in the brain. The article is profusely illustrated by charts, photographs of apparatus and tables. Of this material there is an illustration of a case, severely ill and threatened with eclampsia, where the circulation was studied for a period of eight minutes, during this time the circulation of blood was stopped 63 times, and this was more than half of the entire period.

The Metabolism of Pregnancy.—KNIPPING (*Arch. f. Gynäkol.*, 1923, **116**, 521) has studied the action in pregnant patients of some of the glands of internal secretion. He has especially investigated the anterior portion of the pituitary gland. This he believes causes certain conditions in the metabolism of pregnant patients which develop in the last months. When reproductive life is about to cease, alterations in this portion of the gland are followed by the accumulation in the patient of fat. If his observations are accurate this may give a suggestion concerning the treatment of this condition.

Immunizing against Puerperal Infection.—LOUROS (*Arch. f. Gynäkol.*, 1923, **116**, 589) in the clinic at the University of Athens has endeavored to prevent streptococcus sepsis by injecting vaccines shortly before labor. His results seemed to indicate that the twentieth and tenth day before labor are the best times for this treatment and that from 250 to 500 million bacteria may be given. No failures are reported by the writer, but the interesting question arises as to how he can be positive that his method has absolutely prevented infection, when infection in cases handled with reasonable care, is comparatively infrequent.

The Relation between Polycythemia and Hypercholesteremia in Pregnancy.—BENDA (*Arch. f. Gynäkol.*, 1923, **116**, 506) has studied this subject and has reached conclusions which seem of particular value. Unquestionably during the last weeks of pregnancy cholesterin is increased in quantity in the patient's blood; this increase goes steadily

on until labor; by the eighth day after labor there has been a marked decrease. The red blood cells vary greatly in different patients at the end of pregnancy. The increase in the red blood cells is not the result of concentration of the blood; it is not usual to find elementary forms of red blood cells in the blood stream of pregnant patients. When polycythemia is present the quantity of cholesterin in the blood is increased; there seems to be a relation between this condition and the number of red cells. The cholesterins apparently lessen or inhibit somewhat the physiological hemolytic process in the red blood cells; this has also to do with the condition of the medulla of the bones, and the number of red blood cells during pregnancy is the result of a correlation of activity between those organs in the body which tend to produce and those which tend to destroy the red cells.

The Effect of the Roentgen-ray upon the Ovaries and upon Impregnation and Gestation.—LaCassagne and Coutard (*Gynécol. et Obst.*, 1923, No. 1) contribute a paper upon this subject in which they describe experiments upon animals and the examination of tissues taken from these animals. From these experiments they find that irradiation of the ovaries of a rabbit, if one application is made of no great strength, still produces upon the ova a very definite lesion, this lesion has not been fully described and cannot be demonstrated by microscopical examination of the follicle; it varies in intensity with the degree of radio sensibility possessed by the different primary follicles at the moment of application and is especially pronounced when the roentgen-ray is employed just as the follicles are becoming mature. The result of this is to hinder the development of the ovum in various ways. In some instances atresia of the follicle was produced, the ovum did not become fecundated; in others, there was absence of nidation, the embryo died and fetal death resulted, and the young when born died at term or perished some weeks after birth. If one can apply the results of experiments upon animals to human beings it is fair to suppose that the roentgen-ray may produce similar results in man. Evidently the treatment of metrorrhagia in young women by the roentgen-ray should be conducted with great caution, and while it is essential to check hemorrhage, it is of more importance not to disturb the normal functions of the ovaries. The organs of the rabbit are peculiarly appropriate for such experiments because they closely resemble those of the human subject in their anatomy and physiology.

Cervical Placentæ. — Freund (*Ztschr. f. Geburts.*, 1923, **85**, 581) draws attention to the treatment of cervical placenta. He believes that not only is the ovum in its abnormal attachment the essential feature, but that the condition of the uterine wall is also of importance. The villi of the chorion will attach themselves to any surrounding tissues and the degree of the attachment will depend somewhat upon the character and condition of this tissue. When circumstances are favorable, the villi frequently develop in great depth, and this is especially true in cervical placenta where the villi assume an almost destructive character. That the internal os can be covered by chorionic villi seems to be demonstrable. The fact that hemorrhage begins at varying periods in labor in these cases is due to the depth of penetration of the

placental villi into the substance of the cervix. The intensity of bleeding will depend upon the depth of penetration and the abundance of the placental tissue. Cervical placenta he considers the most dangerous of all forms of placenta previa. In a series of 25 published cases the maternal mortality was 80 per cent. Bleeding often follows the first vaginal examination which should arouse suspicion of a cervical placenta. There are frequently varicose veins in the cervix and surrounding tissues which readily bleed upon examination. The writer reports the case of a primipara, aged forty-three years, in the seventh month of pregnancy who on admission to hospital was found to have two varicose veins of considerable size extending across the anterior lip of the cervix. There was a cervical placenta and the patient had suffered from hemorrhage; bimanual version was then performed but extraction was delayed. The patient rallied well from the first hemorrhage but forty-five minutes later had a sudden collapse without external bleeding. As the anemia was rapidly progressing abdominal Cæsarean section was at once performed, a seven months' dead child removed and considerable blood which had extravasated was removed from the uterus. The placenta could not be separated from the cervix and the effort to do this tore through the cervical wall so that the operator was obliged to perform total extirpation, the patient died of anemia four hours later. In the matter of treatment the writer urges that all vaginal examinations and manipulation, including the use of the tampon, be forbidden outside of hospital. He believes that the low form of section is indicated and he has had excellent results with the old classic operation as well. In the discussion, the majority of opinion favored delivery by section and agreed in emphasizing the fact that these cases must not be disturbed outside of the hospital.

GYNECOLOGY

UNDER THE CHARGE OF

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Radium Needles in Cancer.—Over three years of study and clinical experience with radium needles have led CLARK (*Am. Jour. Roentgen.*, 1923, **10**, 204) to the recognition of the following facts concerning this form of radium application: When radium needles are introduced into neoplastic tissue the maximum reaction is obtained owing, in the first place, to the direct action of the rays upon the tissues, and in the second place, to the cross-fire effect from needle to needle. The total radiation from each needle can be utilized locally in contradistinction to the extravagant dissemination in the air by approxi-

mately three-fourths of the radio-activity during surface application. The corrosive action of the body fluids on the steel needles as originally provided has been largely overcome by the use of nickel alloy. In some cases, however, platinum or irido-platinum needles are more desirable although these are less durable and bend more easily. In addition to the strength of the metal employed in the composition of such needles, an important factor is its property of filtering out the beta rays or all but the hardest beta rays, depending upon the thickness and density of the metal employed. The fact that some of the beta rays are filtered out by the needle walls has been found to be of advantage, since the same therapeutic result can be obtained without as great an inflammatory reaction and after-discomfort to the patient as when all the beta rays are employed. Also, there is less danger of subsequent formation of undesirable slough. By the use of radium in needles and the judicious consideration of this property of filtration, a dose can be given which will exert a lethal action upon malignant cells without causing necrosis with sloughing, but rather a retrogression of the growth and relative conservation of the normal cellular elements. The general appearance is that of mummification, rather than the usual necrotic changes. A small quantity of radium, from 1 mgm. to 10 mgm. in each needle, can be used to even greater advantage than a larger quantity, for the reason that this greater concentration will be more likely to produce sloughing, while the desired effect is to change the character of the cells and render them innocuous by atrophy, also secure final replacement by fibrous connective tissue. Such quantities of radium in needles inserted at equidistant points throughout a growth will, by crossfire action, result in homogeneous radiation over a wide area, while a single capsule or needle containing a large quantity of radium, whether buried in the growth or applied to the surface, will exert its greatest influence at the point of contact, its effect growing rapidly less potent as the distance from the radium is increased. Dosage is all-important in radium needle application and is most difficult to estimate. Important points to be considered are: The anatomical location of the neoplasm, its type and its grade of malignancy. For example: The uterus will stand a larger radium dosage than the rectum; the breast than the buccal surface, the tongue, the floor of the mouth and the tonsil; the stomach more than the intestine, etc. The requirements of the individual case must also be studied. A correct technic is therefore of the utmost importance. With good judgment and such technic, most gratifying results will often be obtained, but should mistakes be made in any of these several factors much damage and suffering may result. For example, too small a dose may only stimulate the neoplasm, while an overdose may result in such dense fibrosis that circulation in the mass is totally arrested. Then within a few weeks or months sloughing will occur, resulting in an ulcer which will not heal. This condition is as bad, though benign, as the one originally present. It has been Clark's experience that needles containing 10 mgm. of radium should not be inserted into a malignant growth at a distance greater than 25 mm. apart, as a lethal effect, from this standpoint, will not be produced beyond this distance. In some instances the distance should be even less, depending upon the degree of radiation concentration desired, the exact amount of radium in each needle, and also the time

allotted for the treatment. Needles with cutting trocar points have been found to be more generally useful than those with round tapering points. A trocar is used before the insertion of a needle if the tissue is dense, but if of soft consistency, the needle may be inserted directly into the tissue. The secondary radiation from metal in contact with the tissues beneath the surface does not produce such an acute reaction as does contact of the metal upon the skin surface. The patient should be prepared as for any surgical operation, since infection may occur if the field is not sterile. The needles may be inserted, as a rule, under local anesthesia. Where, however, many needles are to be employed, or there is any other contraindication to the use of local anesthesia, such as a supersensitive or nervous patient, general anesthesia may be induced.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Experimental Gangrene.—The majority of attempts to produce gangrene in animals with spirochetes and fusiform bacilli have failed. Since it is commonly accepted that gangrenous necrosis occurs only in tissue previously devitalized, KLINE (*Jour. Infect. Dis.*, 1923, **32**, 481) conducted a series of observations on guinea-pigs by inoculating material containing spirochetes and fusiform bacilli into the hind extremities, one of which had been previously traumatized by repeated clamping with a hemostat. By this procedure, he was able to obtain gangrenous necrosis on the injured side in 78 per cent of cases. The experiments included 62 animals. In one group, material from pulmonary gangrene containing innumerable spirochetes, fusiform bacilli and other bacteria was passed from guinea-pig to guinea-pig producing typical gangrene in the thirty-sixth generation. In another group similar material was injected into 2 guinea-pigs in the routine manner and into 1 rabbit intrabronchially. From the same case material from a carious tooth showing organisms similar to those in the gangrenous lung was injected also in 2 guinea-pigs in the usual manner and into 1 rabbit intrabronchially. All the guinea-pigs showed marked gangrenous necrosis on the traumatized side and the rabbits, dying in nine days, showed extensive gangrenous pleuropulmonary lesions. In a third group, material from 4 cases of Vincent's angina containing spirochetes and fusiform bacilli was injected in the routine manner into 4 guinea-pigs, resulting in typical gangrene in 3. The author concludes that "the experimental production in the rabbit of pulmonary gangrene with material from a carious tooth containing spirochetes and fusiform

bacilli is further evidence that the aspiration of these organisms from lesions in the mouth of human beings may lead to pulmonary gangrene."

A Bacteriological Study of Vulvo-vaginitis of Children.—Vulvo-vaginitis in girls of school age leads to exclusion from school, based on the belief that the infection is gonorrheal. In order to ascertain the bacteriological flora of this condition, ANDERSON, SCHULTZ and STEIN (*Jour. Infect. Dis.*, 1923, **32**, 444) made a detailed bacteriological study of 42 school girls up to fifteen years of age with inflammation about the vulva. Direct smears, cultures and immunological reactions comprised the technic. Of the 42 cases, 35.7 per cent were found to be due to the gonococcus and 64.3 per cent were non-specific. In 53.3 per cent of the specific cases the gonococcus was isolated in pure culture, while in the remainder the specific diagnosis was based on the presence within leukocytes of morphologically typical, Gram-negative diplococci, indicating that the direct smear examination should be given preference over the cultural method as a diagnostic procedure. It was impossible by immunological methods to differentiate the gonococci isolated from children from those derived from women. In the non-gonorrheal cases a mixed flora was present, but streptococci of intestinal origin appeared to be the most important agents. Staphylococci, colon bacilli and Gram-positive bacilli were encountered frequently. The authors believe that uncleanliness and local irritation are the important, and probably the primary, factor in the non-specific cases, which were more amenable to therapeutic measures than the gonorrheal cases. They believe, also, that quarantine and exclusion from school are not necessary in the non-gonorrheal cases.

Studies in the Nature of Bacillus Acidophilus Therapy.—In order to study the influence of chemical and physical factors, KOPELOFF and BEERMAN (*Proc. Soc. Exper. Biol. and Med.*, 1923, **20**, No. 8, 425) centrifuged *B. acidophilus* milk and filtered it through a Mandler diatomaceous candle, thus altering its chemical constituents but little. When fed to constipated patients it was practically without effect. Regular *B. acidophilus* milk ingested subsequently resulted in an increase in the number of normal defecations. When *B. acidophilus* milk was sterilized and lactic acid added, thus approximating the original chemical composition, and when fed to constipated patients, little change was noted. The authors believe that these data indicate that *B. acidophilus* therapy is essentially bacteriological rather than physical or chemical in nature.

The Presence of Bacteria in the Lungs of Mice Following Inhalation.—As considerable discussion has arisen at various times as to whether inspired bacteria reach the lungs or are filtered out in the nasal passages, STILLMAN (*Jour. Exper. Med.*, 1923, **38**, 117) conducted a number of experiments on mice in the hope of obtaining further information concerning pulmonary infection under normal conditions. The mice were allowed to inhale an atmosphere in which a fine mist had been produced by spraying a culture of organisms to be studied. As a rule the mice were removed from the spray box one hour after spraying and were killed at various intervals, cultures being made in broth from the lungs,

heart's blood and spleen. The total number of mice exposed to a spray containing virulent hemolytic streptococci was 45, those exposed to a spray containing influenza bacilli was 32 and those exposed, similarly, to staphylococci was 10. It was found that the bacteria, under the conditions of experimentation, readily penetrated into the lower respiratory tract. Pneumococci usually disappeared within a few hours and gave rise to no infection. Hemolytic streptococci, on the other hand, persisted in the lung for a considerably longer time and a general septicemia usually followed. Attempts to determine the conditions under which pneumococci which have reached the lung by inhalation may induce a local or general infection were not successful.

Experimental Production of Streptococcus Endocarditis with Glomerular Nephritis.—Recognizing the extremely high mortality in human subacute streptococcus endocarditis and that the mechanism of production of this disease in human beings depends on two constant factors—injury to the valve with subsequent infection, KINSELLA and SHERBURNE (*Proc. Soc. Exper. Biol. and Med.*, 1923, **20**, 252) were able to produce a bacterial endocarditis and glomerular nephritis in dogs by injuring the aortic valve by inserting an appropriate instrument into the left carotid and, after recovery, injecting green streptococci intravenously. The bacterial vegetations on the aortic valve leaflets were identical with those encountered in human patients. Only those dogs which lived longer than fourteen days showed the glomerular lesion, which consisted of a partial thrombosis of the tuft with hyaline degeneration, hemorrhage and polymorphonuclear leukocytic infiltration. The authors believe that they "have reproduced a bacterial infectious disease which is of sufficient duration to permit thorough study of many of the unknown factors of infection and immunity."

The Susceptibility of Cells to Radium Radiations.—As shown by experiments with paramecium and other protozoa, the response of cells to radium radiations is influenced by the temperature of the cells at the time of radiation and the permeability of the cell membrane. PACKARD (*Proc. Soc. Exper. Biol. and Med.*, 1923, **20**, 226) exposed paramecia, which were descendants of a single wild cell, to radium, amounting to 13.4 mg. of element. The radium was enclosed in a thin-walled glass capsule, and was held at a distance of 2 mm. from the water containing the cells. It was found that cells were more susceptible to radiations at the upper limit of their physiological range of temperature than at their lower limit. At 14° C. the lethal dose was about ten hours; at 37° C. it was one and a half hours. For each rise of 8° C. the length of the lethal dose was halved. The curve expressing these relations was the same as that which expressed the relation between temperature and rate of metabolism in paramecium as shown by the rapidity of cell division and of the pulsation of the vacuoles. Cells whose membranes are relatively permeable were more susceptible to radiations than those whose membranes were relatively impermeable, as determined by the rate at which dilute NH_4OH entered the cells and decolorized the neutral red by which they were stained. Radiation increased the permeability of the cells by injuring the cell wall. If the treatment were continued long enough the cells cytolyzed

completely. "From this it follows that when cells are already highly permeable as they are during growth and division, complete cytolysis quickly ensues; whereas when the cell membrane is relatively impermeable, as it is in resting cells, radiation must be long continued before destructive cytolysis can be observed."

Intestinal Flora in Diarrhea.—"It is generally recognized that the feeding of grain foods and other carbohydrates, particularly lactose and dextrin, to normal animals favors a predominance of aciduric bacteria in the feces, while the feeding of animal proteins favors the development of proteolytic organisms." By applying methods used by others in studying the effects of diet on the fecal flora, HINES (*Jour. Infect. Dis.*, 1923, **32**, 280) ascertained the flora of the feces from 10 normal persons, from 8 individuals with evidence of organic lesions in the intestinal canal and in 9 with diarrhea, 3 of whom were diagnosed "fermentative diarrhea." The proportion of aciduric bacteria to proteolytic ones was determined by the method of Cannon—the so-called colon-acidophilus ratio. Particular attention was paid to *B. Welchii*. It was found that the fecal flora of all normal stools was proteolytic in type and that the spores of *B. welchii* were present in 9 of 10 cases. In the 8 cases who had diarrhea as a result of intestinal lesions, ulcerative or otherwise, the findings were very similar and differed in no way from those of normal stools, other than a definite increase of *B. welchii* spores. On the other hand 2 cases of "fermentative diarrhea" yielded an aciduric flora, whereas a third similar case was proteolytic in character. Spores of *B. welchii* abounded in stools with a proteolytic flora and were absent in those with an aciduric flora.

HYGIENE AND PUBLIC HEALTH

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Tuberculosis: Its Predisposing Causes.—SMITH (*Public Health Reports*, 1923, **38**, 777) shows the danger of infection in childhood and urges that children should be kept away from acute cases of the disease. It is stated that over 1,000,000 people in the United States are constantly sick with tuberculosis and some "carriers" exist. The almost universal infection of people is mentioned, weakened resistance, lack of proper food, exhaustion, bad air, influence of occupation, race, climate, age, predisposing diseases, and alcohol and tobacco are appraised and the following summary given: At an early age practi-

cally all people have become slightly infected with living tubercle bacilli. This fact need not cause alarm, because it probably gives a slight degree of protection against a subsequent infection. Safety, however, depends on the maintenance of a high degree of body resistance to prevent these latent bacilli from producing active tuberculosis. This is not to be accomplished by becoming an athlete, but by the daily observance of general hygienic principles throughout life. Keep the body well nourished, avoid great fatigue, work and sleep in well-ventilated rooms, in freely flowing air and spend as much time as possible outdoors; but carefully reserve hours for adequate rest, as well as for recreation, practise deep breathing and proper carriage, avoid other diseases as far as possible, and be temperate in all things.

The Prevention of Simple Goiter.—KIMBALL (*Public Health Reports*, 1923, **38**, 877) gives briefly the distribution of goiter in various parts of the world, then discusses the relation of iodine deficiency to the disease, after which data in the shape of figures and diagrams are presented to show the benefits that may be expected from the systemic use of iodine, conducing with the following summary: In these endemic goiter districts, if every woman would keep her thyroid saturated with iodine during every pregnancy she would not develop goiter, nor would there be any tendency toward goiter formation in the thyroid of her child. This would save two of the goiter periods in the life of any woman. Then, if every girl would keep her thyroid saturated with iodine during adolescence, that is, from the age of eleven to sixteen years inclusive, none would develop goiter. As to the prevalence of goiter in boys, the following facts are pertinent: (1) Goiter is at least six times more frequent in girls than in boys. (2) A large majority of goiters in boys are congenital and could be prevented by the administration of iodine to the mother during pregnancy. (3) While occasionally a boy does develop goiter at puberty, or after illness, or as the result of some chronic infection, in most cases the goiter will disappear if it is treated promptly and properly. We feel, therefore, that the maximum good from a minimum effort would be gained by applying the principle of goiter prevention to girls as a public health measure. This can best be done through our public school organization; and the education on this subject will ensure application of this method of goiter prevention in later life. The prevention of goiter during pregnancy necessarily depends on the medical profession and on the education of the people as a whole. Each family physician and obstetrician should make this an important part of the routine care of every patient; and the diffusion of this knowledge must be such that each expectant mother will anticipate such care.

Biological Evidence for the Inheritability of Cancer in Man.—SLYE (*Jour. Cancer Res.*, 1923, **7**, 107) states that cancer and non-cancer tendencies segregate out and are transmitted as such. They are therefore unit characters. A specificity of tissue type in specific organs from ancestor to offspring segregates out and is transmitted as such. It is therefore a unit character. Since these things are unit characters, it is possible to manipulate them by selective breeding and thereby to implant them indelibly in any species or to eliminate them perma-

nently and completely from any species. Cancer and non-cancer behave like the absence and presence respectively of a mechanism fitted to control proliferation and differentiation in regenerative processes, and an animal either has this mechanism or lacks it, no matter to what species he may belong. There is therefore a ready and certain genetic method of escape from cancer for the individual and for the race. The demonstration of the inheritability of cancer and non-cancer tendencies in mice is a demonstration of the inheritability of these tendencies in man and in all other species which show cancer, if we are to maintain the theory of evolution and to admit that there is such a thing as biological law. The study of a cancer behavior, which has demonstrated itself to be fundamentally a biological problem, makes evident the necessity of understanding and considering the biological facts underlying all pathological conditions. And, therefore, when we have properly placed biology under all our pathology and bacteriology, all our physiology and therapy, there will no longer be these monstrous diseases, but only the slow and natural death which is the fatigue and diminution and final cessation of the organ and the organism. From the procedure of analyzing stock into its unit characters in order to manipulate cancer tendency, there has emerged the fundamental law of heredity. What goes into the germ plasm must come out in the offspring.

Vincent's Angina and Noma. Experimental Gangrene.—KLINE (*Jour. Inf. Dis.*, 1923, **32**, 481) points out that the majority of attempts to produce gangrene in animals with spirochetes and fusiform bacilli have failed. Veszpremi believes that when the viability of tissue is diminished by disease, the organisms living in the neighborhood, including Spirochæta gracili, increase enormously in number. There is also an increase in the virulence of the organisms and the process takes on a progressive character with the penetration of spirochetes into the tissue prepared for it. The spirochetes are aided by the fusiform bacilli, and under the influence of the cladothrix and other bacteria the characteristic foul-smelling gangrene follows. Since it is commonly accepted that gangrenous necrosis occurs only in tissue previously devitalized, it was decided to traumatize tissue before inoculating the material containing spirochetes and fusiform bacilli. Kline states that in the presence of devitalized tissue, gangrene may be produced in guinea-pigs with material from dental caries and pyorrhea alveolaris, Vincent's angina and pulmonary gangrene containing spirochetes and fusiform bacilli. The experimental production in the rabbit of pulmonary gangrene with material from a carious tooth containing spirochetes and fusiform bacilli is further evidence that the aspiration of these organisms from lesions in the mouths of human beings may lead to pulmonary gangrene.

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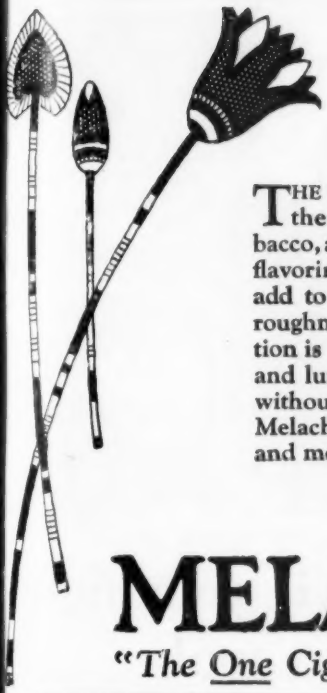

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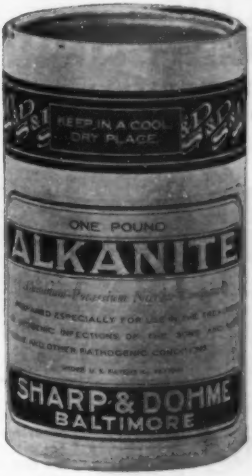

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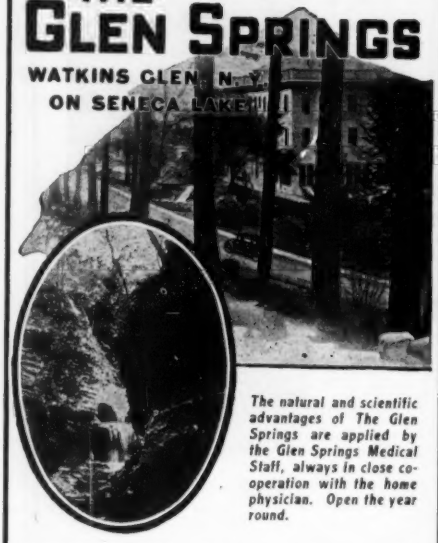

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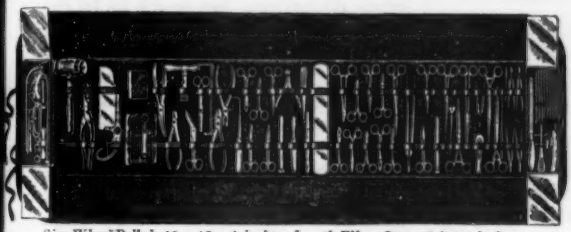

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Forceps, curved bone-gouging, with spring	1
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Scissors, heavy blunt	1
Scissors, bandage	1
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Forceps, bone-gouging, without spring	1
Hernia needle, blunt	1
Forceps, clamp compression, Pean's	1
Forceps, haemostatic, straight small jaw	3
Scissors, curved	1
Gag, mouth, Denhardt	1
Chisel	1
Enucleator, Young's	1
Curette, mastoid	1
Dissector and raspatory	1
Bone spatula	2
Forceps, clamp 6 in.	1
Needle holder	1
Haemostatic forceps, straight	6
Forceps, tissue	1
Forceps, dressing	1
Scissors, dressing, blunt ends	1
Scissors, dressing, pointed ends	1
Gouge	1
Clamp, compression, intestinal, Murphy	2
Director, grooved and aneurism needle	1
Forceps, dissecting	3
Tongue depressor, folding	1
Forceps, Jones, 2-inch bite	2
Probe and director, straight	1
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Gigli saws	6
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Trocar	1
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Handles for Gigli saws	2
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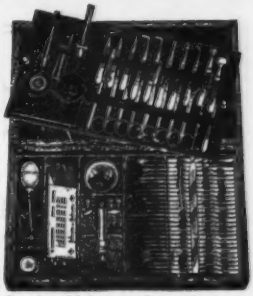

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Forceps, entropium, Desmarres's	1
Forceps, fixation, with catch	2
Forceps, iris, angular, mouse-toothed	2
Forceps, needle-holding, Steven's	2
Forceps, trachoma, Moyes's, 1 up and 1 down	2
Forceps, trachoma, Prince's	1
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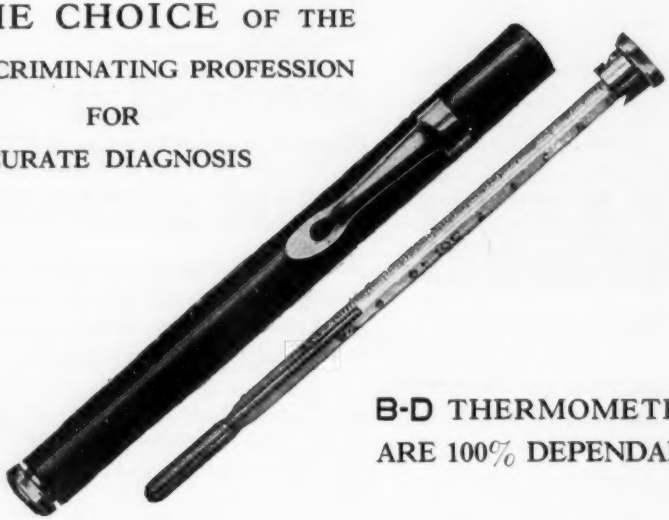

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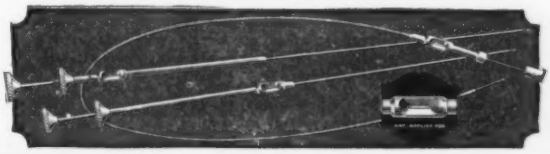

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